

Recurrent myocardial infarction associated with gefitinib therapy

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Abstract Gefitinib is an epidermal growth factor tyrosine kinase inhibitor used as a targeted chemotherapeutic agent in the treatment of lung cancer and other solid malignancies. Unlike other tyrosine kinase inhibitors, gefitinib is not recognized as having significant cardiotoxicity though it has been reported to be capable of potentiating ADP-induced activation and thromboxane A_2 generation in platelets which could promote thrombosis. We report a case of recurrent myocardial infarction with angiographically documented vulnerable plaque rupture in a patient receiving chronic gefitinib therapy for metastatic carcinoid tumor. Platelet function studies revealed marked ADP-induced platelet activation that was only suppressed by high-dose clopidogrel. Measurement of urine 11-dehydrothromboxane B_2 also indicated persistent thromboxane A_2 generation despite aspirin therapy, an emerging risk factor for adverse cardiovascular events.

Keywords Gefitinib · Myocardial infarction ·
Plaque rupture · Thromboxane · Platelets

Background

Gefitinib is a targeted chemotherapeutic agent that inhibits tumor cell proliferation and survival by blocking epidermal growth factor tyrosine kinase (EGF-TK) [1]. Initially approved for the treatment of non-small cell lung cancer, it is now being evaluated for the treatment for a variety of

solid tumors [2]. Gefitinib is administered orally and is generally well-tolerated. Common side effects include anorexia, diarrhea, acne-like rash and mild-moderate elevation of hepatic transaminases [3]. Administration of low-dose aspirin therapy has been shown to ameliorate some of these side effects [4]. Gefitinib is not known to be associated with significant cardiotoxicity that has been observed with other tyrosine kinase inhibitors, such as heart failure, conduction abnormalities or thrombosis [5]. We report a case of recurrent myocardial infarction in a patient with metastatic carcinoid tumor treated with gefitinib.

Case report

The patient was a 47-year-old man in 1993 with no significant prior medical history when he underwent right hemicolectomy for abdominal pain and bowel obstruction. The pathology revealed a multicentric carcinoid tumor involving the ileocecal valve and appendix with metastases to regional lymph nodes and peri-intestinal soft tissue. Two years later he underwent exploratory laparotomy for abdominal pain and was found to have recurrent disease involving the anterior abdominal wall. This was resected and he subsequently underwent chemotherapy with streptozocin and doxorubicin. Serial CT scans performed over the next several years demonstrated slowly progressive disease with hepatic and pulmonary metastases. In 2004, he was started on 40 mg octreotide monthly and relatively large doses of ibuprofen for persistent fever, body aches and night sweats. In 2005, he was started on gefitinib 250 mg daily as part of a phase II clinical trial. An echocardiogram obtained immediately prior to the start of treatment revealed an ejection fraction of 55% without wall motion or valvular abnormalities. He tolerated gefitinib

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therapy well and serial CT scans performed over the ensuing years revealed no significance progression in tumor burden.

In October 2008, at the age of 62, he developed crescendo angina. During an exercise stress test, he developed severe chest discomfort at a maximum workload of 8.0 METS associated with 2–3 mm ST segment depressions on ECG. The chest discomfort persisted into recovery and he was referred for urgent cardiac catheterization. At the time of admission, the patient was on his 42nd monthly cycle of gefitinib, did not smoke and had never had hypertension or diabetes. His fasting lipid profile on no lipid-lowering therapy was notable for LDL and HDL cholesterol levels of 98 and 44 mg/dl, respectively. His family history was notable for a father who was a heavy smoker and died of a myocardial infarction at age 57. Coronary angiography revealed a long 95% hazy stenosis of the proximal left anterior descending (LAD) coronary artery with moderate stenoses of the mid and distal vessel (Fig. 1a). There were no significant stenoses observed in either the left circumflex or right coronary arteries. Aspirin, clopidogrel, unfractionated heparin and eptifibatide were administered and the culprit proximal LAD stenosis was successfully

stented with an everolimus drug-eluting stent with an excellent angiographic result. The initial cardiac enzymes were positive with a CPK-MB of 14 µg/l (normal range 0–7 µg/l) that peaked at 36 µg/l after the procedure. Discharge medications included aspirin 325 mg daily, clopidogrel 75 mg daily, pantoprazole 40 mg daily, and pravastatin 40 mg daily in addition to his preadmission medications of ibuprofen, gefitinib, and octreotide.

One week after stent placement, the patient experienced atypical chest discomfort associated with facial numbness, lightheadedness, and shortness of breath. The ECG was unremarkable. Repeat coronary angiography revealed a widely patent stent in the proximal LAD with no significant changes elsewhere (Fig. 1b). Tests were performed to evaluate the patient’s responsiveness to aspirin and clopidogrel (Table 1). While there was suppressed platelet aggregation to arachidonic acid (3%) and a prolonged PFA-100 collagen/epinephrine closure time (>300 s) suggesting an appropriate aspirin-mediated antiplatelet effect, urine level of 11-dehydro-thromboxane B₂ was elevated (>1500 pg/mg creatinine), indicating persistent thromboxane generation despite aspirin therapy. There appeared to be an adequate antiplatelet effect of clopidogrel based on

Fig. 1 Coronary arteriograms obtained **a** at the initial presentation showing a complex 95% stenosis of the left anterior descending coronary artery (LAD *black arrow*). **b** 1 week after successful LAD stent implantation, **c** 6 weeks after LAD stent implantation showing plaque rupture causing a new 95% lesion in the left circumflex coronary artery (LCX *white arrow*), and **d** immediately following successful circumflex stent implantation

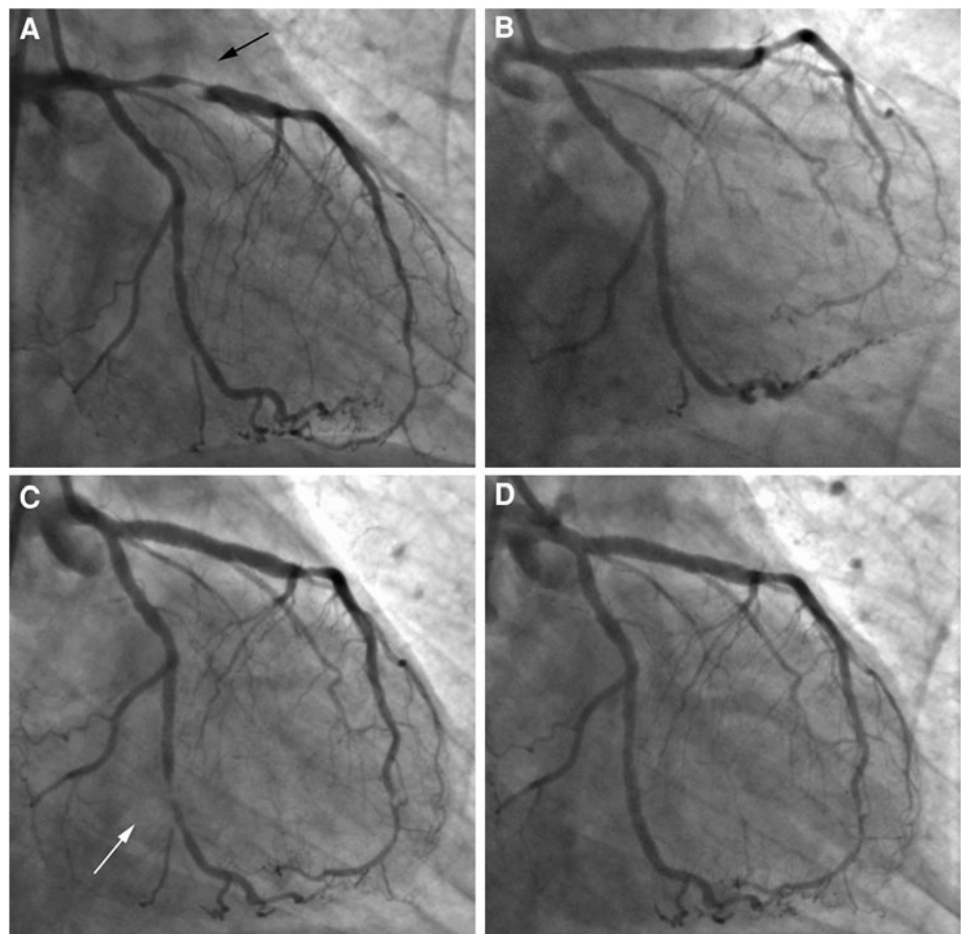


Table 1 Laboratory parameters

Assay	325 mg ASA ± 75 mg clopidogrel	325 mg ASA ± 150 mg clopidogrel	Reference Range
Light transmission platelet aggregometry (maximum % platelet aggregation)			
Arachidonic acid (0.5 nM)	3	–	<20 ^a
ADP (5 μM)	78	0	<50 ^b
ADP (10 μM)	72	0	<70 ^b
ADP (20 μM)	–	45	<70 ^b
Epinephrine (10 μM)	48	–	78–88
Collagen (5 μg/ml)	85	–	70–94
PFA-100 closure time (s)			
Collagen/ADP	123	108	71–118
Collagen/epinephrine	>300	>285	>193 ^a
VerifyNow P2Y12 assay			
Base result	276	297	–
PRU result	144	121	<240 ^b
Inhibition (%)	48	59	–
Urine 11-dehydro-thromboxane B ₂ (pg/mg creatinine)	2440	–	<1500 ^a

ADP adenosine diphosphate,
PRU P2Y12 reaction unit

^a Target range on aspirin
therapy [17]

^b Target range on clopidogrel
therapy [9]

the VerifyNow P2Y12 assay (<240 PRU), though by light transmission aggregometry there remained robust platelet aggregation in response to 5 and 10 μM ADP (>70%). Based on this, the clopidogrel dose was increased to 150 mg daily. Repeat platelet function testing performed one week after increasing the clopidogrel dose revealed no platelet aggregation in response to 5 and 10 μM ADP and <50% aggregation in response to 20 μM ADP.

The patient was well until 6 weeks after LAD stent placement when he developed severe substernal chest pain at rest. Although the ECG revealed non-specific ST segment changes, he ruled in for a myocardial infarction with a peak CPK-MB fraction of 41 μg/l. Coronary angiography revealed a widely patent stent in the proximal LAD. There was, however, a new 95% hazy stenosis in the circumflex marginal coronary artery (Fig. 1c) at the site of a non-significant narrowing observed on the previous angiograms. The new culprit lesion was successfully stented with an everolimus drug-eluting stent with an excellent angiographic result (Fig. 1d). Transthoracic echocardiography demonstrated a left ventricular ejection fraction of 45–50% with inferolateral akinesis. The gefitinib was discontinued.

Over the subsequent 2 years, the patient has not had any recurrent cardiovascular events and an interval dobutamine stress echocardiogram revealed no evidence of inducible ischemia. He continues on aspirin 325 mg daily, clopidogrel 150 mg daily, octreotide 40 mg monthly and ibuprofen as needed to control persistent fevers and body aches. Serial CT scans reveal no significant progression of hepatic and pulmonary metastatic disease.

Discussion

We report the first case of recurrent coronary thrombosis in a patient undergoing treatment with gefitinib. Based on the Naranjo et al. [6] adverse drug reaction probability scale, the association can be classified as possible. At the time of the index cardiovascular event, our patient had only a moderate 10-year cardiovascular risk with a Framingham risk score of 11%. Yamaguchi et al. [7] previously reported a case of myocardial infarction in a 75-year-old woman with a history of diabetes and hypertension 2 months after initiating treatment with gefitinib for relapsing lung adenocarcinoma. In contrast to that report, our patient underwent serial coronary angiography which revealed the second myocardial infarction to have been clearly caused by the rupture of a vulnerable atherosclerotic plaque in a vessel with minimal prior luminal narrowing.

Although a direct causal relationship cannot be established, there is intriguing circumstantial evidence suggesting gefitinib might be capable of increasing the risk of myocardial infarction. In a study of 20 aspirin-naïve patients, Nomura's group found that gefitinib appeared to potentiate ADP-induced platelet activation [8]. One week after LAD stent implantation, our patient manifested surprisingly robust ADP-induced platelet activation despite being on clopidogrel 75 mg daily. Such high on-treatment platelet reactivity is a recognized risk factor for both stent thrombosis and recurrent myocardial infarction [9]. Fortunately, ADP-induced platelet activation was significantly suppressed after doubling the clopidogrel dose to 150 mg daily.

Nomura's group also showed that gefitinib significantly increased the capacity of platelets to generate thromboxane A₂ (TXA₂) during clot formation as measured by serum levels of its stable metabolite, thromboxane B₂ (TXB₂) [4]. Aspirin, which suppresses platelet TXA₂ formation by irreversibly inhibiting the cyclooxygenase-1 (COX-1) enzyme, significantly reduced serum TXB₂ levels in these patients. Arachidonic acid-induced platelet aggregation is known to be inhibited when platelet TXA₂ generation is suppressed >90% by aspirin [10, 11]. Our patient had essentially no arachidonic acid-induced platelet aggregation, indicating a high degree of platelet COX-1 inhibition by aspirin. Despite this, urine levels of the TXB₂ metabolite, 11-dehydro-TXB₂, were significantly elevated in our patient (>1500 pg/mg creatinine). Unlike levels of serum TXB₂, urine 11-dehydro-TXB₂ levels reflect TXA₂ synthesis that occurs throughout the body, not just in platelets. In addition to stimulating COX-1-mediated TXA₂ synthesis in platelets, it is conceivable that gefitinib also potentiates TXA₂ synthesis from non-platelet sources, such as via an inducible COX-2 pathway in inflammatory and endothelial cells. Whatever the source, persistent TXA₂ generation despite aspirin therapy is emerging as a potent cardiovascular risk factor. In a cohort of 3,261 subjects enrolled in the CHARISMA trial on aspirin who were randomized to clopidogrel or placebo, subjects with the highest quartile of urine 11-dehydro-TXB₂ at baseline had a 1.7-fold increased risk (CI 1.1–2.6, $P = 0.03$) of myocardial infarction, stroke and cardiovascular death at 28 months compared to those with the lowest quartile of UTXB₂ [12]. Our group also recently found that aspirin-insensitive thromboxane generation was associated with a 2.6-fold (CI 1.2–5.6, $P = 0.015$) increased odds of early vein graft thrombosis after coronary artery bypass surgery [13].

It is also conceivable that gefitinib may have contributed to vulnerable plaque rupture in our patient. EGF is a potent chemoattractant and mitogen for vascular smooth muscle cells whose expression is increased in human atherosclerotic plaques [14] and induced after arterial balloon injury where it mediates neointima formation [15]. Smooth muscle cells are a major source of collagen synthesis and are thus critical to maintain the integrity of the fibrous cap of atherosclerotic plaques [16]. Gefitinib is known to be capable of inhibiting EGF-induced smooth muscle cell proliferation [15] and thus may impair the integrity of the fibrous cap leaving atherosclerotic plaques more prone to rupture.

In conclusion, we report an intriguing case of recurrent myocardial infarction in a patient with metastatic carcinoid tumor treated with chronic gefitinib therapy. The known biologic effects of the EGF signaling pathway raise the possibility that an EGF-TK inhibitor such as gefitinib could predispose to atherothrombosis. Further studies are needed

to determine if gefitinib use is associated with an increase risk of adverse cardiovascular events and the mechanism by which this might occur.

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