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CLINICAL CASE CHALLENGES

OCT-Based Management of Nilotinib-Associated CAD in a Patient With Chronic Myeloid Leukemia

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Chronic myeloid leukemia (CML) is a myeloproliferative disorder of pluripotent hematopoietic stem cells caused by Bcr-Abl tyrosine kinase, the product of the Philadelphia chromosome. Bcr-Abl tyrosine kinase inhibitors (TKIs) have dramatically improved the prognosis of patients with CML (1). Although ~ 20% of patients with CML develop intolerance or resistance to the first Bcr-Abl TKI, imatinib mesylate, several second-generation TKIs, including nilotinib, dasatinib, and bosutinib, have overcome this issue (2).

However, second-generation Bcr-Abl TKIs are associated with an increased risk of arterial thromboembolic events such as coronary artery disease (CAD), ischemic stroke, and peripheral arterial disease. In particular, nilotinib has a significantly higher risk of CAD compared with imatinib (3). The mechanisms of arterial disease are not well understood, thus leading to knowledge gaps in the prevention and optimal treatment of nilotinib-associated CAD in clinical practice.

Optical coherence tomography (OCT) allows real-time and high-resolution visualization of microstructures of coronary plaques that are undetectable by other intravascular imaging modalities (4), and it is widely applied for the diagnostic assessment of CAD. Here we report a case of a male patient with CML and nilotinib-associated CAD who benefited from the use of OCT to identify coronary artery thrombosis in a nonculprit lesion.

CASE PRESENTATION

A 66-year-old nonsmoking male patient was diagnosed with CML in 2012. He had a history of hypertension, dyslipidemia, and diabetes mellitus. His blood pressure was controlled at 120/80 mm Hg with valsartan 80 mg, carvedilol 10 mg, and amlodipine 10 mg daily. His low-density lipoprotein cholesterol was approximately 70 mg/dl with rosuvastatin 5 mg daily. Diabetes mellitus was controlled by diet therapy, and his hemoglobin A1c was 6.5%. He had not undergone any previous cardiovascular procedures before the start of CML therapy. Induction therapy with 300 mg of nilotinib twice daily led to a major molecular remission after 6 months, and he was continued on this dose. An electrocardiogram (ECG) 7 days before the treatment and periodic ECGs every 3 months showed no abnormalities and a normal QT interval.

In December 2017, after taking nilotinib for 5.7 years, the patient complained of chest pressure on mild exertion. Although an ECG and stress ECG did not reveal any abnormalities, he was admitted to the hospital with suspected unstable angina pectoris. His hematologist changed nilotinib 300 mg twice daily to dasatinib 50 mg twice daily just before admission over concern of a nilotinib-associated vascular adverse event. Consistent with the patient's angina-like symptoms, coronary angiography revealed stenoses in the left and right coronary arteries, with a SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score of 20 points. Dual antiplatelet therapy (DAPT) with aspirin (100 mg daily) and prasugrel (3.75 mg daily) was initiated. The proximal portion of left anterior descending artery was believed to be the

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culprit lesion because this lesion was most severely stenotic. Percutaneous coronary intervention (PCI) to the stenoses in left anterior descending artery and high lateral branch was performed without any complications. During the PCI of the left coronary artery, we used intravascular ultrasound (IVUS). This imaging modality showed large mixed plaques, including a lipid-rich core and low-attenuated plaque in the culprit lesion.

Three days later, we performed PCI to the right coronary artery. The moderately stenotic lesion by angiography extended from segment 1 to 2 according to the modified American College of Cardiology and American Heart Association guidelines (Figure 1). IVUS demonstrated mixed plaques of diffuse lengths with a minimal lumen area of 2.0 mm^2, suggestive of a significant stenosis. We also performed OCT for a detailed investigation of the pathophysiology of coronary disease. Here, a signal-rich and low-backscattering projection was detected that was indicative of a thrombus in a portion of the right coronary artery interposed between the stenotic lesions (Figure 2). This had not been detected by IVUS. Accordingly, we deployed 2 sirolimus-eluting stents (Ultimaster 3.5×38 mm and 4×28 mm, Terumo, Japan) to cover all the lesions and achieved an optimal result. The patient had no symptoms after PCI with DAPT. He also remained in remission of CML, and no adverse events occurred under dasatinib treatment.

Six months after PCI, we performed repeat coronary angiography, in consideration of a higher risk of in-stent restenosis as a potential complication of Bcr-Abl TKIs. Angiography did not suggest any in-stent restenosis or new lesions. We further performed OCT of the left and coronary arteries and confirmed there was sufficient neointimal coverage of the stents and no de novo coronary thrombosis. On the basis of these findings, we transitioned the patient to single antiplatelet therapy. The prospective course was uneventful with aspirin 100 mg daily and dasatinib 50 mg twice daily.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CML = chronic myeloid leukemia

DAPT = dual antiplatelet therapy

ECG = electrocardiogram

IVUS = intravascular ultrasound

OCT = optical coherence tomography

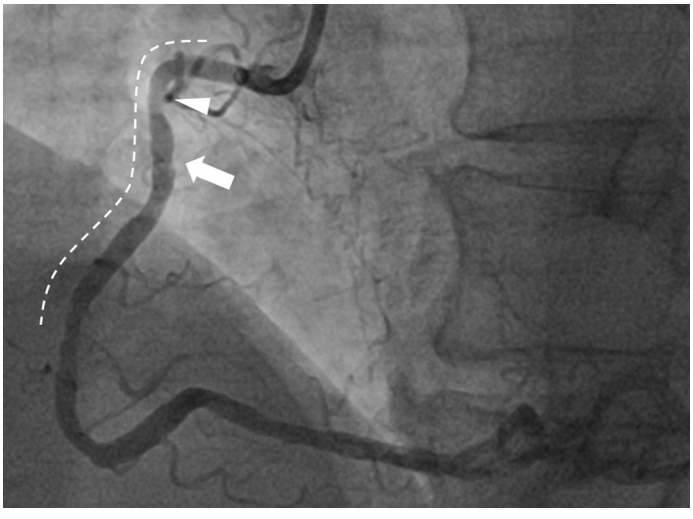
PCI = percutaneous coronary intervention

TKI = tyrosine kinase inhibitor

DISCUSSION

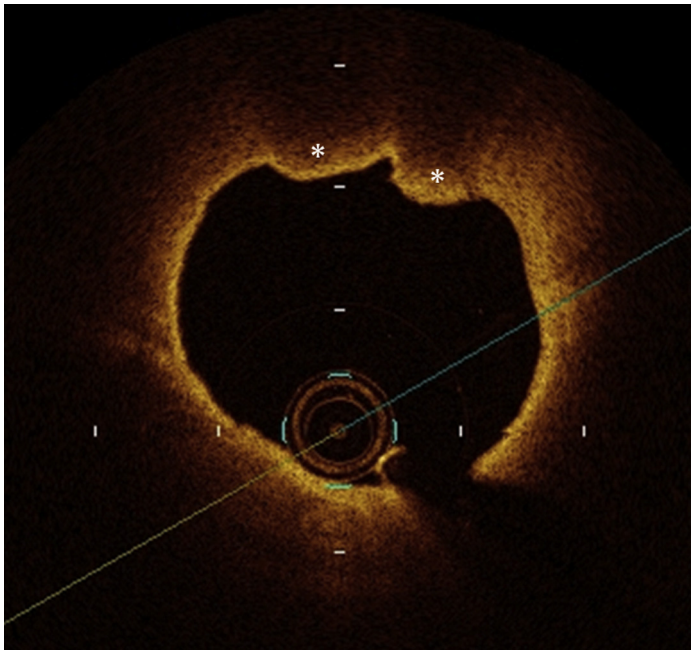
Bcr-Abl TKIs have improved the prognosis of patients with CML dramatically, but prolonged administration of Bcr-Abl TKIs, particularly nilotinib, has been associated with adverse cardiovascular events (3). We report a case of an older male patient with CML who had significant CAD during nilotinib treatment. To the best of our knowledge, this is the first case reporting the use of OCT in the diagnostic assessment and therapeutic

FIGURE 1 Coronary Angiography Showed a Stenotic Lesion That Extended From Segment 1 to 2 in the RCA



Optical coherence tomography was performed along the **dotted line.** The **arrowhead** indicates the significant stenotic lesion in angiography. The **arrow** indicates the site where the optical coherence tomography image in Figure 2 was obtained. RCA = right coronary artery.

FIGURE 2 Coronary Thrombus Detected by OCT Showed Silent Coronary Thrombus in a Nonculprit Lesion, Which Was Not Detected on IVUS



IVUS = intravascular ultrasound; OCT = optical coherence tomography. The asterisk (*) indicates that a silent thrombus in the portion of right coronary artery.

management of coronary lesions during nilotinib treatment. Two findings in the pathological evaluation by OCT were noted. First, OCT during PCI revealed coronary thrombosis incidentally. Second, OCT during follow-up coronary angiography revealed complete neointimal coverage of the implanted stents, and we switched from DAPT to single antiplatelet therapy on the basis of this finding.

The mechanisms underlying the cardiovascular complications associated with Bcr-Abl TKIs are not fully elucidated. In patients with CML who are treated with nilotinib, conventional cardiovascular risk factors such as diabetes mellitus, dyslipidemia, obesity, smoking, and hypertension are associated with a higher risk of atherosclerotic events (5), whereas vascular adverse events sometimes occur in patients even in the absence of risk factors. In this case, the patient had some risk factors for CAD, which were well controlled by diet or medical therapy. We hypothesize that the formation of significant coronary stenoses was accelerated by treatment with nilotinib. Mechanistically, nilotinib may exacerbate coronary risk factors such as dyslipidemia or diabetes and promote the development of coronary plaque (6). In addition, nilotinib may exert a detrimental effect on endothelial cell function (7) by activating adhesion and aggregation of platelets (8). Although all Bcr-Abl TKIs share potent inhibitory activity against the Bcr-Abl tyrosine kinase, they have distinct pharmacological properties on other vascular system kinases such as vascular endothelial growth factor receptors, Tie-2, platelet-derived growth factor receptors, and fibroblast growth factor receptors (9). Further investigations are required to elucidate whether the detrimental sequelae of nilotinib treatment on the vasculature are related to off-target effects, and which kinases are involved in the adverse effects of nilotinib on glucose and lipid metabolism and homeostatic regulation of endothelial cells and platelets.

Importantly, in this case, application of intravascular OCT was effective in the detection of coronary thrombosis and in guiding decision-making during PCI in a patient with CML who was treated with nilotinib. We consider OCT to be an ancillary imaging modality useful for discriminating the characteristics of coronary lesions in patients with CML who are treated with nilotinib and other Bcr-Abl TKIs. When coronary stenosis is mainly caused by formation of atherosclerotic plaques (6), treatment should be strengthened for management

of coronary risk factors such as diabetes mellitus and dyslipidemia, in addition to coronary intervention. However, when the coronary stenosis is mainly caused by thromboembolic factors (7,8), it may be desirable to switch from nilotinib to other Bcr-Abl TKIs with a lower probability of thromboembolic adverse events and to initiate antiplatelet or anticoagulant therapy (9). In clinical practice, both mechanisms, accelerated atherosclerosis and thrombus formation, contribute to the pathogenesis of coronary stenosis, but OCT helped guide rational treatment in our case.

We note that the most effective approach for revascularization in nilotinib-associated CAD is still unknown. In this case, we selected PCI, and not coronary artery bypass grafting, for revascularization according to the SYNTAX score (10). Further accumulation of clinical evidence is required to determine whether PCI or coronary artery bypass grafting is optimal for better outcomes in patients with nilotinib-associated CAD.

It is also important to note that OCT during follow-up angiography was used to confirm sufficient neointimal coverage after implantation of the drug-eluting stents. Bcr-Abl TKIs impair endothelial cell proliferation and migration, and a potential delay in neointimal coverage is a concern. The optimal duration of DAPT in patients treated with Bcr-Abl TKIs is currently unclear because of the lack of clinical evidence; however, we believe that OCT is a reliable imaging modality for confirmation of complete neointimal coverage of stents during follow-up coronary angiography and to guide the transition from DAPT to single antiplatelet therapy. Further studies using OCT technology are required to elucidate the effects of Bcr-Abl TKIs on neointimal coverage of stents and to determine the optimal duration of DAPT after stent implantation.

CONCLUSIONS

Cardiovascular adverse events with nilotinib are of growing importance. The standardized treatment for coronary adverse events remains undetermined, but this case indicates that OCT is a useful intravascular imaging modality to discern the characteristics of coronary lesions during PCI and to evaluate neointimal coverage of stents. This information obtained during follow-up angiography was used to de-escalate dual to single antiplatelet therapy. Further studies are needed to establish evidence of the utility of OCT during PCI in patients with CML who are treated with Bcr-Abl TKIs.

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