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An Intra-procedural Stent Thrombosis in a Prasugrel Resistant Patient Treated with Ticagrelor

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Stent thromboses due to multifactorial causes including hypercoagulable conditions and high on treatment platelet reactivity (HTPR), which means a low response to anti-platelet therapy, especially clopidogrel. Prasugrel is a third generation thienopyridine and inactive pro-drug requiring metabolic activation in vivo, which improves the rate of HTPR with clopidogrel. This drug is mostly effective, with a potent, fast, and consistent anti-platelet action, but rare cases of inadequate platelet inhibition with prasugrel have been reported. Here we describe the case of a 47-year-old man who presented with a recurrent acute myocardial infarction and ST during an intravascular ultrasound pullback and was resistant to prasugrel, was successfully treated with ticagrelor.

Key Words: Prasugrel resistance, Stent thrombosis, Ticagrelor

Introduction

Stent thromboses (STs) are generally known to be increased in the setting of acute coronary syndrome (ACS), diabetes mellitus, stents in bifurcation sites, and the discontinuation of anti-platelet therapy [1]. STs have become a major safety concern after percutaneous coronary intervention (PCI) [2]. High on-treatment platelet reactivity (HTPR) also is due to multifactorial causes, but it is now known that loss-of-function polymorphisms in cytochrome P450 (CYP) 2C19 are the strongest individual variables affecting the anti-platelet action of clopidogrel [3,4]. Because prasugrel has a single CYP dependent oxidative step, this drug is expected to be more effective and have a lesser variable inhibition of the

platelet function than clopidogrel [3]. However, despite its greater anti-platelet potency compared with clopidogrel, recent investigation has shown that some of patients treated with prasugrel may still have HTPR and the risk of ischemic complications [5]. The pathophysiology of STs in patients with hypercoagulable conditions is unclear, but there have been several studies on the potential role of a hypercoagulable condition in STs. We introduced a case of intra-procedural stent thrombosis (ST) during an intravascular ultrasound (IVUS) pullback, which represented a hypercoagulable condition and HTPR despite taking prasugrel for 6 months that was successfully overcome by ticagrelor and oral anticoagulant.

Case Report

A 47-year-old man who had no risk factors for coronary artery disease except for a high body mass index (BMI) value (27 kg/m^2) visited our outpatient clinic with effort-related chest pain. He had a previous PCI history of an ST-segment elevation myocardial infarction (STEMI) 6 months prior, and the coronary angiography (CAG) at that time revealed a significant stenosis in the proximal portion of the left anterior descending artery (pLAD) of 99%, middle portion of the LAD (mLAD) of 80%, proximal portion of the left circumflex artery (pLCX) of 50%, and distal portion of the LCX (dLCX) of 70% (Fig. 1A). Balloon angioplasty with subsequent deployment of an everolimus-eluting 2.75 × 38 mm stent (Promus Element®, Boston Scientific, Natick, MA, USA) was performed in the pLAD. The patient had been taking dual anti-platelet agents (aspirin 100 mg with prasugrel 10 mg daily) for 6 months.

The electrocardiogram at our clinic did not show

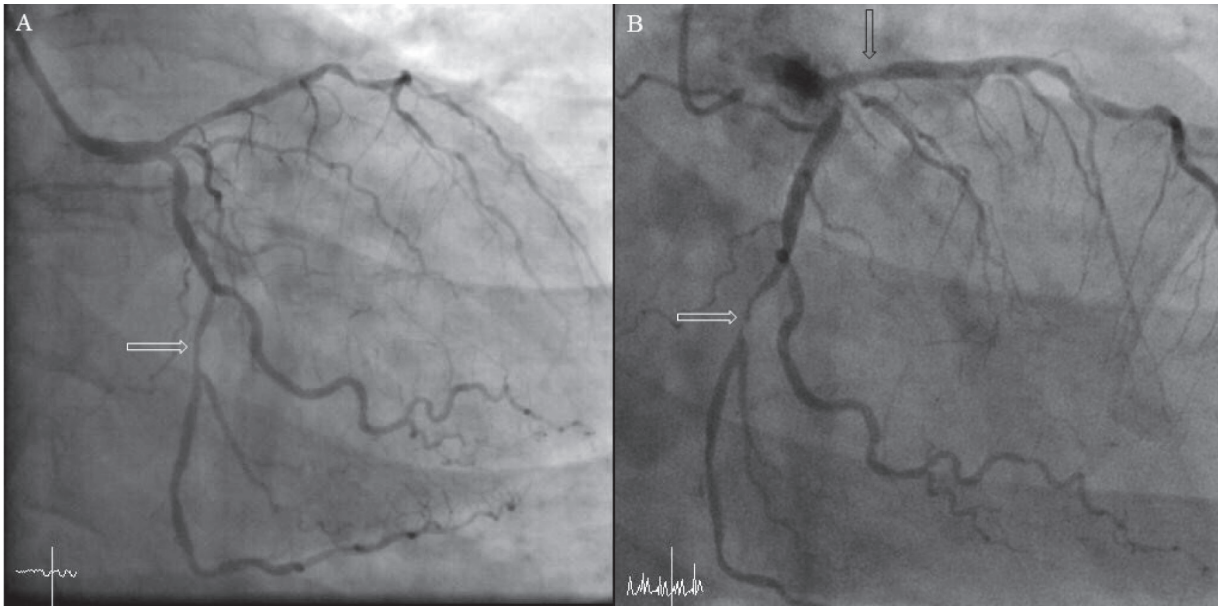

Fig. 1. (A) Coronary angiography at 6 months ago shows significant stenosis in pLAD 99%, mLAD 80%, pLCX 50% and dLCX 70%. (B) Coronary angiography at admission shows no in-stent restenosis of previous stent inserted site (black arrow), but white arrow showed progressive stenosis of dLCX, 90%. pLAD: proximal portion of left anterior descending artery, mLAD: middle portion of left anterior descending artery, pLCX: proximal portion of left circumflex artery, dLCX: distal portion of left circumflex artery.

any definite ST-segment or T-wave changes, but the blood test for the cardiac enzymes after admission was positive (troponin I 0.717 ng/mL, reference value < 0.056 ng/mL). With a diagnosis of a non-ST-segment elevation myocardial infarction (NSTEMI) of Killip class I (with no clinical signs of heart failure), a loading dose (4,000 units) of unfractionated heparin (UFH), aspirin 100 mg, prasugrel 10 mg, and a high dose statin (atorvastatin 40 mg) was administered prior to the CAG and left ventricular ejection fraction (LVEF) was 64% at admission.

The CAG showed that there was no evidence of any in-stent restenosis (ISR), but progression of the dLCX stenosis (90%) was noted (Fig. 1B). After an additional intravenous administration of UFH (3,000 units), IVUS was performed to evaluate whether the proximal edge of the previous pLAD stent had crossing over the LCX ostium, and there were diffuse thrombi surrounding the IVUS catheter at the left main artery (LM) to the pLAD level (Fig. 2A). During the IVUS pullback in the LCX, an acute thrombosis in the LM with a thrombolysis in myocardial infarction (TIMI) 0 flow occurred (Fig. 2B), and soon after progression of the ST caused a flow compromise of the LAD and LCX, and ventricular tachycardia and ventricular fibrillation occurred. Defibrillation failed to recovery of sinus rhythm, so immediate intra-aortic balloon pumping (IABP) and extracorporeal membrane oxygenation (ECMO) support were performed. Under the IABP and ECMO support, a thrombus aspiration and ballooning angioplasty at the ST site was performed with an immediate improvement in the distal flow. An additional deployment of a sirolimus-eluting 2.5 × 26 mm stent in the mLAD (Orsiro®, Biotronik AG, Bulach, Switzerland) and sirolimus-eluting 2.5 × 18 mm stent in the dLCX (Orsiro®, Biotronik AG, Bulach, Switzerland) was performed, and the final

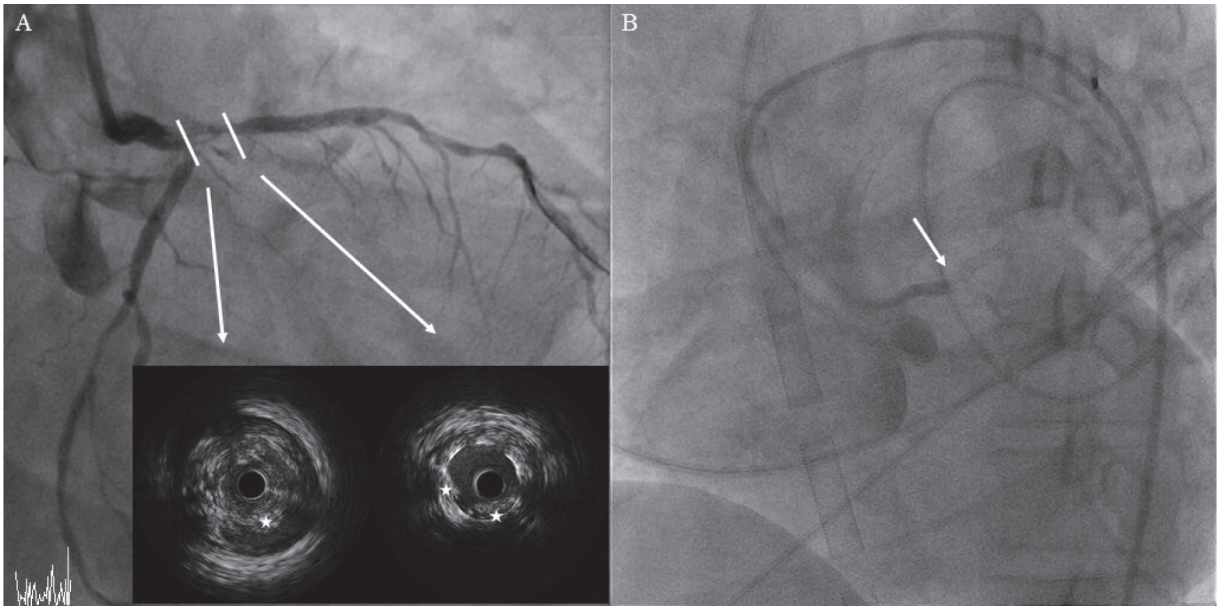

Fig. 2. (A) Diffuse thrombus surrounding IVUS catheter in LM level (asterisk) and thrombus in pLAD level is revealed in IVUS (asterisk). (B) During the IVUS pullback in the LCX, an acute thrombosis in the LM with a TIMI 0 flow occurrs (white arrow). IVUS: intravascular ultrasound, LM: left main artery, pLAD: proximal portion of left anterior descending artery, LCX: left circumflex artery, TIMI: thrombolysis in myocardial infarction.

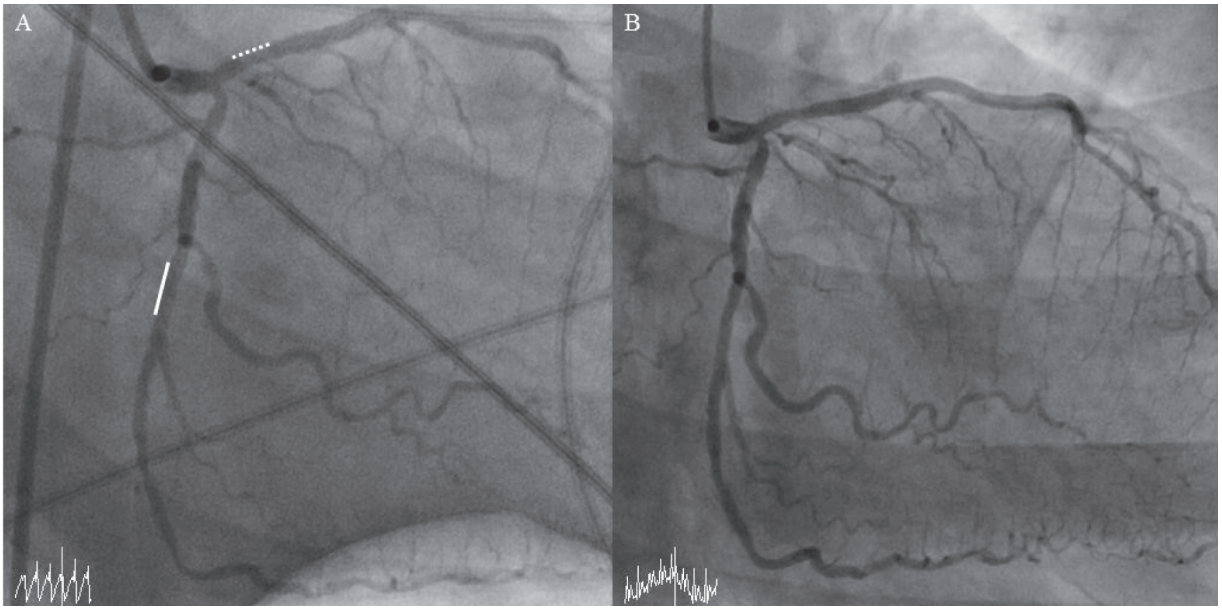

Fig. 3. (A) Final angiography reveals optimal angiographic results with a TIMI 3 flow. (B) There is no evidence of in-stent restenosis upon follow-up coronary angiography 1 year after percutaneous coronary intervention. TIMI: thrombolysis in myocardial infarction.

angiography revealed optimal angiographic results with a TIMI 3 flow (Fig. 3A).

With the intravenous administration of abciximab due to a high thrombus burden and critical course, intensive care under ECMO and ventilator assistance was continued for a persistent myocardial stunning state, and the post-PCI LVEF was 18%. Three days after admission, weaning from the IABP and ECMO was successfully completed.

Four days after admission, although the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA, USA) might have been affected by the abciximab over 14 days, an assay and blood tests for the coagulation factors were performed to evaluate the platelet reactivity and hypercoagulable condition of the patient. Those studies resulted in 0% platelet reactivity unit (PRU) inhibition (PRU value 316) and an abnormal coagulation factor assay; protein C level 75% (reference value 55%~125%), protein S level 50.8% (reference value 55%~160%), factor 7 assay 80% (reference value 70%~130%), factor 8 assay 257% (reference value 60%~140%), and factor 9 assay 182% (reference value 60%~140%). Five days after admission, the patient complained of a tingling sensation in both legs and a brain magnetic resonance imaging revealed multiple tiny acute embolic infarctions. We concluded that the patient was prasugrel resistant and a ticagrelor maintenance dose (90 mg twice a day) was given instead of the prasugrel. Also, based on the patient's hypercoagulable condition and clinical events such as an acute cerebral embolic infarction, anti-coagulation with warfarin was decided with caution, and a therapeutic range for the international normalized ratio (INR) of 1.5 was targeted with aspirin and ticagrelor. Five days after beginning the administration of ticagrelor (9 days after admission), the Verify. Now P2Y12 assay was repeated and the percent inhibition improved to 74% (PRU value 98) (Fig. 4).

Together, we tested the polymerase chain reaction and direct gene sequencing of CYP2C19 to detect any genotype polymorphisms. The patient was revealed

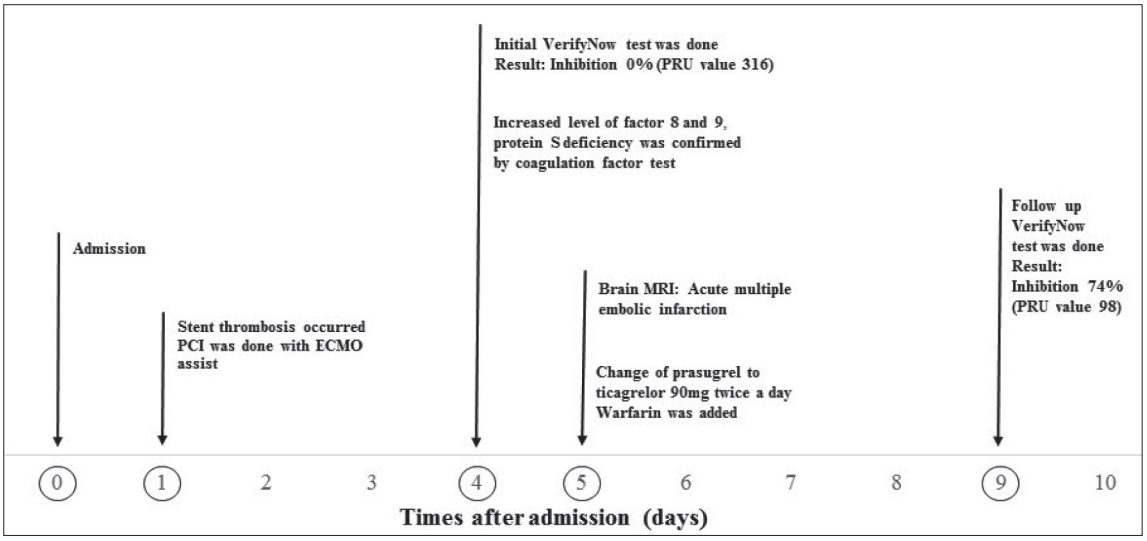

Fig. 4. Main clinical events over times after admission are shown in this figure. In day 1, stent thrombosis during IVUS pullback was occurred despite of taking prasugrel 10 mg for 6 months. At day 4, initial VerifyNow P2Y12 assay showed 0% of PRU inhibition (PRU value 316) and coagulation factor tests revealed increased level of factor 8 & 9 with protein S deficiency. At day 5, the patient complained tingling sensation of both leg and brain MRI showed acute tiny multiple embolic infarction. With cautiously, triple therapy with aspirin, ticagrelor and warfarin was started. At day 9, percent of PRU inhibition recovered to 74% (PRU value 98). IVUS: intravascular ultrasound, PRU: platelet reactivity unit, MRI: magnetic resonance imaging.

to have a heterozygote in CYP2C19*2, which was relevant to an intermediate metabolizer.

He was discharged without any other complications and his LVEF improved to 50%, while taking aspirin 100 mg, ticagrelor 90 mg twice a day, warfarin 1 mg, carvedilol 3.125 mg, rosuvastatin 20 mg, nicorandil 5 mg twice a day, and trimetazidine 35 mg twice a day. The patient has been receiving outpatient treatment with same medications for 1 year without any specific events. After 1 year, follow-up CAG was performed without chest pain and there were no evidence of ISR (Fig. 3B).

Discussion

ST is a major safety issue after a PCI and remains the primary cause of death after a PCI despite suitable anti-platelet therapy and the further development of stent types. ST is a multifactorial problem related to lesions, procedures, the coagulation system, devices, and patient factors such as a high on-treatment platelet reactivity (HTPR) and hypercoagulable condition [2].

There were two possible predictors of the intra-procedural STs in this case HTPR under prasugrel and a hypercoagulable condition. Otherwise, the patient had no predisposing factors for an ST such as a poor compliance, procedural and device factors. Regarding the low responsiveness to prasugrel, the patient had some risk factors such as a high BMI value, ACS, and a genotype polymorphism in CYP2C19 [3].

Prasugrel is a thienopyridine derivative and one of the P2Y12 receptor antagonist, which undergoes hydrolysis and hepatic oxidation, and is mainly related to the CYP3A4, 2B6, and 2C9 isoenzymes, followed by CYP2C19 [4,6]. In this case, a genotype polymorphism only in CYP2C19 was confirmed. The

lack of a whole genetic study for genetic polymorphisms regarding CYP3A4, 2C9, and 2B6 was a limitation of this report, however, though the percent inhibition of the platelet aggregation was extremely low (0%), it could be anticipatable that other major CYP (CYP3A4, 2B6 and 2C9) genotype polymorphisms might have been present. In contrast to prasugrel, ticagrelor is a non-thienopyridine, which directly interacts with the P2Y12 receptors, and changing to ticagrelor in prasugrel resistant patients could be an effective therapeutic option as in this case [7].

Hyperactivity of coagulation factors could also be presumed to have influenced the ST. Praven K. *et al*. showed that a deficiency of protein C or S was known to produce a prothrombotic state, and more than 80% of patients in the ST group had either protein S levels alone or together below normal [8]. Other studies have shown that a low activated protein C level is associated with early myocardial infarctions and with the extent and severity of atherosclerosis [9]. Factor 8 is a non-enzymatic plasma protein necessary for blood coagulation to proceed and serves as a cofactor to enzyme 9a in the activation of factor 10 [10]. Thereby, an increased level of factor 8 can increase the patient's risk for a hypercoagulable condition. In our case, the protein S level was low and the levels of factors 8 and 9 were high. So, it might be assumed that the hypercoagulable condition could have resulted from any other causes that would have affected the intraprocedural ST, and a vitamin K antagonist was used for the correction of the hypercoagulable condition and cerebral embolic infarction. Generally, it is recommended that the therapeutic decision making for a triple therapy consisting of aspirin, a P2Y12 receptor inhibitor, and vitamin K antagonist, requires careful consideration of the increased risk of bleeding in selective patients [11]. Further, there is no definite guidance for the dosage or duration of a combination of aspirin, ticagrelor, and warfarin. Therefore, greater caution to prevent bleeding complications is needed as in this patient.

The ST occurred during an IVUS pullback before the PCI in our case and it is commonly known that IVUS related STs are rare [12]. Although the causal relationship was unclear between the ST during the IVUS pullback and the IVUS in this case, it might be assumed that a long-standing automated pullback procedure under a hypercoagulable condition could irritate any unstable plaque and provoke an ST.

It is generally recommended that a VerifyNow P2Y12 assay should not be performed in patients who have received a glycoprotein (GP) IIb/IIIa receptor antagonist within 14 days of the abciximab [13]. A large thrombus burden and recurrent AMI despite taking prasugrel for 6 months meant that the anti-platelet therapy in this patient was ineffective, and therefore, a potent blockade of the platelet GPIIb/IIIa receptors was needed immediately. Because the assays for the prasugrel and ticagrelor were performed 4 and 9 days after admission, we presumed there was a similar interference by the abciximab on the platelet function in both, translating into the possibility of a low responsiveness to prasugrel.

Cases of treatment with ticagrelor to overcome prasugrel resistance have been reported [14-17]. However, the previously introduced cases differed from ours, with respect to the evaluation of the hypercoagulable condition, exploration of the CYP450 isoenzyme, and presence of critical clinical events such as STs or cardiogenic shock. One case was a patient with an STEMI undergoing a PCI followed by repeated angioplasty after suffering from an early ST and who had a resistant to thienopyridine treatment, and was successfully overcome by switching to the non-thienopyridine class drug, ticagrelor [14].

Despite taking prasugrel for 6 months, a recurrent AMI and intra-procedural ST occurred. Because there

are no definite evidence-based guidelines regarding the management of prasugrel-resistance, our report offers information on a therapeutic option for prasugrel-resistance under a hypercoagulable condition by changing to another class drug, that is, ticagrelor with warfarin.

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