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Brief Report

Clopidogrel resistance in diabetic patient with acute myocardial infarction due to stent thrombosis ☆,☆☆

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ABSTRACT

Stent thrombosis is a morbid complication after percutaneous coronary intervention. Dual antiplatelet therapy significantly reduces stent thrombosis risk and forms currently the basis in acute ST elevation myocardial infarction pharmacologic treatment. The introduction of clopidogrel has made a major advance in the acute coronary syndrome treatment. However, there is growing evidence about failure in antiplatelet response after clopidogrel, which may lead to subsequent risk of future thrombotic events. The antiplatelet inhibitory effect of clopidogrel varies widely among individuals. High on-treatment platelet reactivity has been repeatedly associated with a hazard for cardiovascular events, including stent thrombosis. Laboratory monitoring of antiplatelet therapy efficacy may help identify patients with insufficient antiplatelet response. Prasugrel therapy was repeatedly described as an effective method to overcome clopidogrel resistance. We report a case of diabetic patient in whom myocardial reinfarction due to stent thrombosis developed. Clopidogrel resistance was detected in this patient using light transmission aggregometry and vasodilator-stimulated phosphoprotein phosphorylation assessment. After prasugrel administration, no other ischemic event occurred, and patient was released to outpatient care in good general condition.

1. Introduction

Dual antiplatelet therapy containing aspirin and $P2Y_{12}$ adenosine diphosphate (ADP) receptor antagonist forms currently the basis in acute ST-elevation myocardial infarction (STEMI) pharmacologic treatment. The introduction of $P2Y_{12}$ ADP receptor antagonists has made a major advance in the acute coronary syndrome (ACS) treatment [1]. Stent thrombosis is a morbid complication after percutaneous coronary intervention (PCI). It is more frequently encountered in acute coronary syndrome patients and in patients with diabetes mellitus (DM), bifurcation stents, or in those who discontinue prematurely dual antiplatelet therapy [2-4].

Dual antiplatelet therapy significantly reduces stent thrombosis risk. Nevertheless, there is a wide variability in pharmacodynamic response to clopidogrel administration, which is linked to several factors, including genotype polymorphisms [5]. Nowadays, there is growing amount of data about failure in antiplatelet response after clopidogrel administration, which is specifically associated with insulin resistance and DM [6,7]. This incomplete antiplatelet response may contribute to a worse prognosis of acute myocardial infarction in patients with DM. High platelet reactivity after clopidogrel administration is associated with increased risk of stent thrombosis and other ischemic events [8,9]. High variability in antiplatelet response to clopidogrel administration points to the suitability of laboratory monitoring of antiplatelet therapy efficacy in patients with ACS. Laboratory monitoring of antiplatelet therapy by ex vivo platelet function tests may help identify individuals with poor antiplatelet response [10]. High platelet reactivity after clopidogrel administration represents also major reason for introduction of new $P2Y_{12}$ ADP receptor antagonists with more favorable pharmacodynamic profile to clinical practice [11]. Prasugrel, a new $P2Y_{12}$ ADP receptor antagonist, provides more consistent inhibition of $P2Y_{12}$ ADP receptor and has lower intraindividual variability in efficacy compared with clopidogrel. Benefit of prasugrel therapy seems to be the highest in

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patients with DM [12]. Prasugrel therapy was repeatedly described as an effective method to overcome clopidogrel resistance [13,14].

We report a case of diabetic patient admitted for acute anterior STEMI, in whom myocardial reinfarction due to stent thrombosis occurred. Clopidogrel resistance using light transmission aggregometry (LTA) with specific inducer (10 μmol/L ADP) and vasodilator-stimulated phosphoprotein (VASP) phosphorylation assessment was consequently identified in this patient. After prasugrel administration, no other ischemic event occurred, and patient was in a good general condition released to outpatient care.

2. Case report

Eighty-two-year-old patient with arterial hypertension, type 2 DM in stage of organ complications (diabetic macroangiopathy), treated by oral antidiabetic agents, was admitted to internal department with a diagnosis of acute anterior STEMI to realize urgent coronary angiography. In the prehospital phase, the patient was treated with loading dose of aspirin 400 mg and clopidogrel 600 mg along with 5000 IU of unfractionated heparin intravenously. Urgent coronary angiography revealed acute subocclusion of left anterior descending coronary artery (LAD), which was subsequently treated with primary percutaneous coronary intervention (pPCI) with bare metal stent (BMS) implantation with good angiographic effect (Fig. 1).

On the second day of hospitalization, a strong rest chest pain appeared in patient. Twelve lead electrocardiogram (ECG) previewed ST-segment elevation suggestive of acute re-STEMI of anterior wall (Fig. 2). The patient had been consequently treated with antagonists of glycoprotein IIb/IIIa receptor, and immediately, another urgent coronary angiography was performed. Second coronary angiography found the acute closure of LAD as a result of acute stent thrombosis. Acute closure was being subsequently treated with catheter thrombextraction and with implantation of 2 BMS. (Fig. 3). Because of suspected clopidogrel resistance, antiplatelet treatment with prasugrel was initiated/loading dose of 60 mg followed by a 10 mg/daily maintenance dose.

Examination of the antiplatelet therapy efficacy using LTA with specific inducer and measurement of VASP protein phosphorylation in a blood sample taken before the first coronary angiography (1.5 hours after clopidogrel loading dose administration) revealed the patient's insufficient antiplatelet response to clopidogrel-platelet aggregation after the induction with 10 μmol/L ADP 84% (reference value <50%), the phosphorylation of VASP protein 81% (reference value <50%). Similarly, second examination of antiplatelet therapy efficacy, from the sample taken 1 hour after administration of first clopidogrel maintenance dose (20.3 hours after clopidogrel loading dose administration) and approximately 1 hour before acute re-STEMI development, measured using VASP phosphorylation assessment confirmed patient's insufficient antiplatelet response to clopidogrel-VASP phosphorylation rate 57% (reference value <50%).

After initiation of prasugrel antiplatelet therapy, no further ischemic events during the course of hospitalization developed, and patient was finally hemodynamically stable and in a good overall condition released to outpatient care. Laboratory examination showed good antiplatelet response on prasugrel-VASP phosphorylation rate 26%, LTA after the induction with 10 μmol/L ADP 22% (reference value <50%). Echocardiography revealed a reduced left ventricular systolic function, with an akinesia of anterior and lateral wall, left ventricular ejection fraction was approximately 30%. Despite the patient's high age (which is a relative contraindication for prasugrel treatment), prasugrel therapy was well tolerated, and no bleeding was seen during hospitalization and next 6-month of follow-up.

3. Discussion

Stent thrombosis is a morbid complication after PCI. It is more frequently encountered in patients with ACS and DM, bifurcation stents, or in those who discontinue prematurely dual antiplatelet therapy [2-4]. Dual antiplatelet therapy significantly reduces stent thrombosis risk and forms currently the basis in acute STEMI pharmacologic treatment. The intervention of several complementary ways of platelet activation and aggregation is necessary to ensure effective treatment and prevention of coronary thrombosis. The introduction of $P2Y_{12}$ ADP receptor antagonists has made a major advance in the ACS treatment. Thienopyridine clopidogrel given in the Clopidogrel in Unstable Angina to Prevent Recurrent Events study in patients with ACS significantly reduced the incidence of cardiac death and nonfatal myocardial infarction or stroke compared with patients treated with aspirin alone [1]. A 600 mg clopidogrel loading dose leads to a faster onset of action and has a greater platelet inhibitory effect than a loading dose of 300 mg [15,16]. Although several large clinical trials have demonstrated the efficacy of clopidogrel in the treatment of ACS, there is growing amount of data about failure in antiplatelet response after clopidogrel administration [6,7]. Variability of antiplatelet response (antiplatelet therapy resistance) may lead to antiplatelet therapy insufficient efficacy and subsequent risk of thrombotic events. The antiplatelet inhibitory effect of the thienopyridine clopidogrel varies widely among individuals. This wide variability in pharmacodynamic response to clopidogrel administration is linked to several factors, including genotype polymorphisms [5]. High on-treatment platelet reactivity has been associated with a substantial

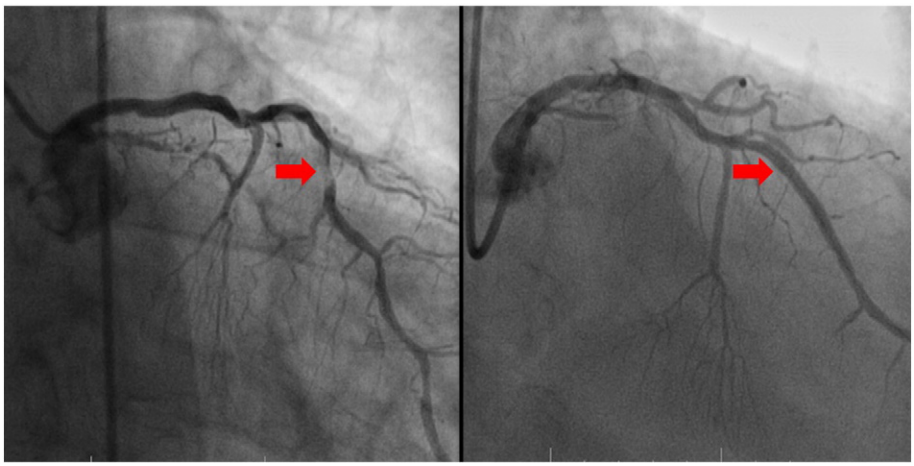

Fig. 1. Urgent coronary angiography in patient with acute STEMI showing an acute subocclusion of LAD and angiography after pPCI on LAD with implantation of BMS.