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High-residual platelet activity despite dual antiplatelet treatment associated with subacute stent thrombosis

Case Report

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Abstract: High-residual platelet activity despite the dual antiplatelet treatment with aspirin and clopidogrel is associated with major adverse cardiac events, including stent thrombosis. Acute and subacute stent thrombosis is rare, but presents itself with serious complications including high mortality and morbidity rates. Light transmittance aggregometry with specific agonists – arachidonic acid and 5-adenosin diphosphate – is still considered a standard for the assessment of platelet reactivity, besides novel methods like vasodilator-stimulated phosphoprotein phosphorylation. In our case study, we report the coincidence of high-residual platelet activity with subacute stent thrombosis despite the recommended doses of antiplatelet agents – aspirin and clopidogrel. Stent thrombosis was treated by aspiration thrombectomy, and antiplatelet treatment was modified by increasing the dose of aspirin and substituting clopidogrel with a first-generation thienopyridin – ticlopidin. The effect of the treatment was documented by reaching the optimal inhibition of platelet reactivity. In the 6- and 12-month follow-up, the patient presented no ischemic events.

Keywords: *Resistance • Dual antiplatelet therapy • Stent thrombosis • Light transmittance aggregometry • Clopidogrel*

1. Introduction

High-residual platelet activity - despite the dual antiplatelet treatment with aspirin and clopidogrel - is closely associated with rare (rate about 1%), but catastrophic complication of stent implantation – subacute stent thrombosis, which would result in a high mortality rate [1]. The assessment of platelet reactivity is not routinely practiced and there are no randomized, placebo-controlled data confirming the direct correlation between high-residual platelet reactivity (confirmed by laboratory assessment) and clinical manifestation of stent thrombosis. The data confirming this hypothesis are mostly derived from registries, non-randomized prospective studies and from one randomized prospective study [2]. We report the coincidence of subacute bare-metal stent thrombosis with low responsiveness to clopidogrel confirmed by light transmittance aggregometry (LTA), which was treated by aspiration thrombectomy and substituting clopidogrel with ticlopidin.

2. Case report

A 52-year-old male, current smoker with no other risk factors was admitted to the hospital due to acute myocardial infarction with ST elevations (STEMI) of the anterior wall as a primomanifestation of ischemic heart disease. He was successfully treated with primary percutaneous coronary intervention (PCI) – occlusion of proximal left anterior descending artery (LAD) by implantation of bare-metal stent Liberté 4.0/20 mm using high-pressure dilation (20 atm). After five days of the index procedure, the patient was discharged. The

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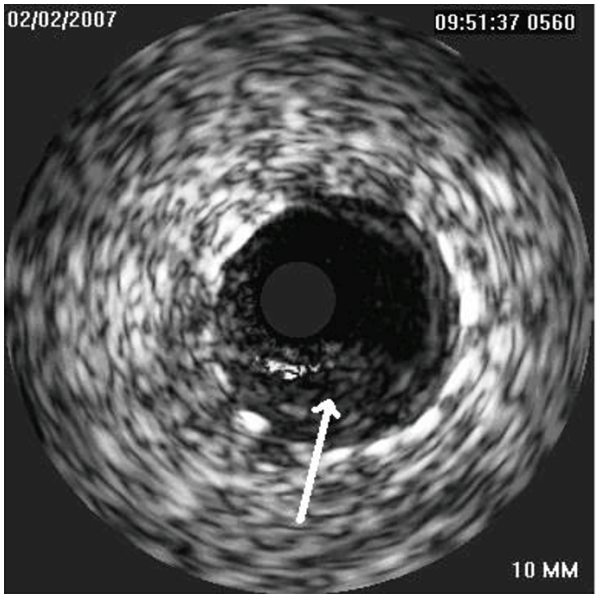
Figure 1. Intravascular ultrasound (IVUS) image of the mural thrombus (arrow) inside the implanted stent.



hospitalization course was without any complications; the patient was treated with 100 mg of aspirin, 75 mg of clopidogrel, 2.5 mg of bisoprolol and 40 mg of simvastatin with no use of calcium channel blockers. The assessment of the left ventricle function was without regional motion abnormalities; the maximum troponin I level was 2.6 ug/l. The following day, the patient was readmitted due to atypical chest pain. There were no ischemic changes on electrocardiogram (ECG); troponin I was negative (<0.2 ug/l). Coronary angiography documented optimal result of preceding intervention. Nineteen days since the stent implantation, the patient was readmitted again due to chest pain with initial negative troponin I value (<0.2 ug/l). Because of the rise of troponin I value (3.004 ug/l) the next morning, immediate cardiac catheterization was done, which revealed partial thrombotic occlusion of the stent implanted in the LAD. Intravascular ultrasound (IVUS) confirmed the presence of mural thrombus (Figure 1), which was successfully withdrawn with aspiration thrombectomy. According to the IVUS, the apposition of the stent was optimal; no edge dissection was detected. During catheterization, a bolus of 20 mg of abciximab was given followed by a 12-hour infusion of 10 mg, and a weight-adjusted dose of enoxaparin was subsequently given. LTA was done with inductors: arachidonic acid (ARA) to monitor the effect of aspirin treatment, and 5-adenosine diphosphate (ADP) to monitor the effect of clopidogrel treatment. After ARA inductor, the inhibition of platelet aggregation reached only 58% (residual aggregation 42%), and after ADP inductor, only 33% (residual aggregation 67%) (Figure 2). The cutoff point for effective treatment with aspirin was considered in reaching at least 80% inhibition [3], and for clopidogrel treatment at least 50% [4]. According to these results, we have decided to increase the dose of oral aspirin to 400 mg daily, and to displace treatment with clopidogrel by ticlopidin in a daily dose of 500 mg. After 5 days of

Figure 2. Light transmittance aggregometry (LTA) results for arachidonic acid (ARA) and 5-adenosine diphosphate (ADP)-like agonists of platelet aggregation. At that time the patient was treated with aspirin 100 mg and clopidogrel 75 mg.

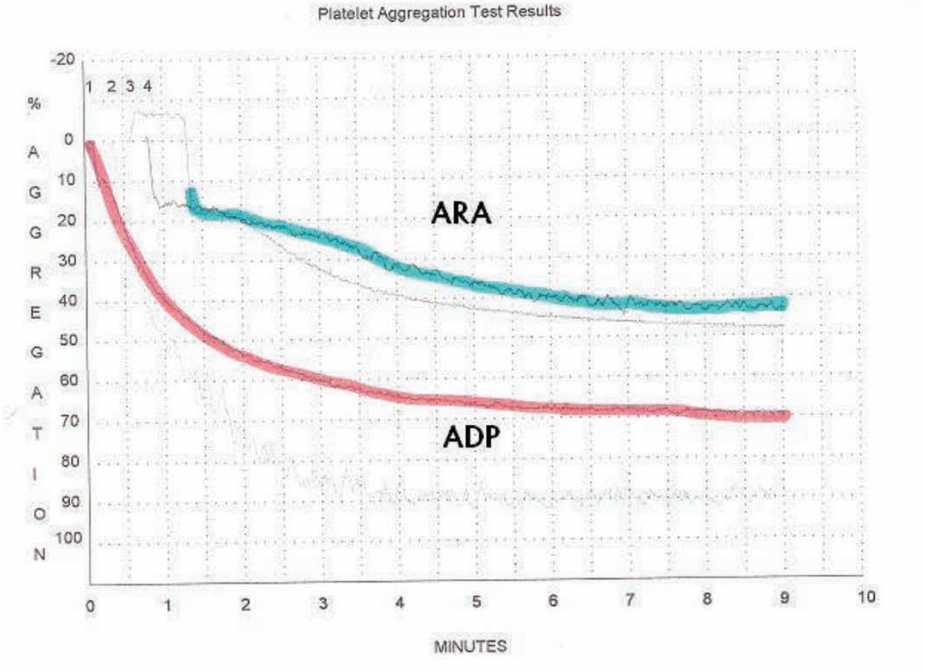
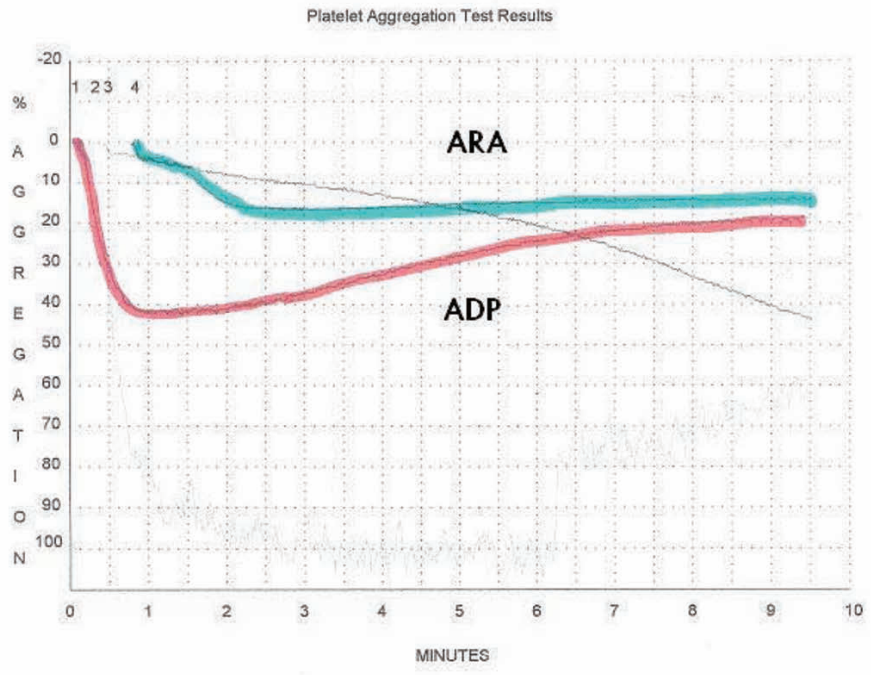


Figure 3. Light transmittance aggregometry (LTA) results for arachidonic acid (ARA) and 5-adenosine diphosphate (ADP)-like agonists of platelet aggregation. At that time the patient was treated with aspirin 400 mg and ticlopidin 500 mg.



treatment with an increased dose of aspirin and 500 mg of ticlopidin, the LTA was repeated. Platelet aggregation after ARA inductor reached 87% inhibition (residual aggregation 13%), and for ADP inductor to 82% (residual aggregation 18%) (Figure 3).

After 6 months of dual antiplatelet therapy, the treatment with ticlopidin was discontinued with ongoing antiplatelet treatment with 400 mg aspirin. In the 6- and 12-month follow–ups, the patient showed no clinical signs of ischemia and with negative stress test.

3. Discussion

We reported the case of subacute stent thrombosis despite its optimal implantation. The reason was resistance to the dual antiplatelet treatment, mainly low responsiveness to clopidogrel. There was also low responsiveness to the acetylsalicylic acid (dose 100 mg p.d.) which was increased to 400 mg p.d. Subacute stent thrombosis occurs in approximately 0.5–1% of implanted stents [5,6], and one of the reasons considered is high residual platelet activity [7,8]. There are many factors involving the platelet reactivity [9-11] and one must be very cautious in interpreting the results. Despite mentioned limitation this complication has a frequent catastrophic course with a high mortality rate [1], and thus it represents a significant risk for patients treated with stent implantation.

Despite the issue is of great research interest and extensive investigations reported in the past several years, many unresolved problems still remain. At first, because of its rarity of occurrence, there are no randomized, placebo-controlled data, and all data have to be polled from registries and prospective trials. Secondly, there has been no consensus as to which method is to be used as a “gold standard” for platelet reactivity assessment. Thirdly, what is the frequency of resistance, and how are these results translated into the clinical outcomes?

Since the pioneering works in the nineties, the dual antiplatelet treatment has been considered the cornerstone in the prevention of stent thrombosis [12-14]. Despite the accessibility of this treatment, there is still a cohort of patients with major cardiovascular events after successful treatment, and these events seem to be associated with low antiplatelet effect of clopidogrel [7,15,16]. Response variability and resistance to clopidogrel therapy was first reported in 2003 [17]. Since then, many studies and registries suggested a relationship between high post-treatment platelet reactivity and clopidogrel nonresponsiveness in patients undergoing PCI, especially increased ischemic events including stent thrombosis [7,8,18,19]. All these data are from retrospective and prospective studies.

The optimal method of determining in vivo function of the platelets through ex vivo testing is still under debate [20]. For the purpose of monitoring clopidogrel resistance,

LTA and vasodilator-stimulated phosphoprotein (VASP) index were used. Aggregation determined by LTA has been used as a "gold standard" and is based on the stimulation of platelet-platelet aggregation in platelet-rich plasma after stimulation with agonists [21]. A modified version of LTA is impedance aggregometry, which uses whole blood samples, in that aggregation is measured by impedance, not light transmittance [22]. The main limitation is no standard value or threshold verified in clinical trials for the level of the aggregation blockage in association with clinical events. The VASP determination is based on intracellular signaling. VASP is phosphorylated by protein kinases that are activated by cyclic adenosine monophosphate. With flow cytometry it is possible to quantify the amount of phosphorylated VASP and measure unblocked $P2Y_{12}$ [23].

The frequency of non-responsiveness to clopidogrel varies according to the threshold of the definition. In recent LTA studies, for stent thrombosis ≥40%, and for ischemic events within 6 months ≥50% of inducible platelet aggregation after stimulation by 20 µl/l ADP, is considered a relevant value [4,8]. It is thus necessary to achieve more than 50% inhibition of aggregation to optimize the clinical outcome after coronary stenting. In one study, the cutoff point was established for low responders as a 70% resting aggregation after 20 µl/l ADP stimulation (30% of inhibition), and again a significant difference was found in the clinical outcome in a six-month follow-up [18]. If one may accept this threshold as a reference for resistance, the incidence seems to vary about 10%-20% in stable coronary artery disease, but reaches almost 50% in acute coronary syndromes [2]. In a study on the impact of dual non-responsiveness and the drug eluting stent implantation on the incidence of stent thrombosis, this dual non-responsiveness was identified in 6% of patients [24].

In a recently published randomized, prospective trial, platelet reactivity was assessed by VASP index [2]. High-risk patients with refractory angina pectoris and non-ST-segment elevation myocardial infarction (NSTEMI) were included in the study. The VASP index was measured 24 h after the first 600-mg bolus of clopidogrel. All patients with a VASP index above 50% (threshold for insufficient platelet inhibition) were randomized to the control group (n = 84) and to the VASP-guided group (n = 78). In the control group, PCI was carried out without an additional bolus of clopidogrel. In the VASP-guided group, three additional boluses (300 mg) of clopidogrel were given to achieve a VASP index below 50%. Finally, despite an extremely high dose of clopidogrel, 14% of patients (n = 11) randomized to the VASP-guided group were still resistant with a VASP index above 50%. All the eight major adverse cardiac events (MACE) (10%) occurred during the one-month follow-up in the control group, including the five related to stent thrombosis.

This study raises a question still under debate: if and how to modify the therapy in patients identified as non-responders to treatment with clopidogrel. There are four possibilities to manage such patients: to continue the treatment with a standard dose of clopidogrel; to increase the dose of clopidogrel; to switch the treatment to ticlopidin; or to switch the treatment to prasugrel.

According to the data mentioned so far, high-residual platelet activity is strongly associated with MACE, including stent thrombosis, and so it is advisable to measure platelet activity routinely and try to achieve effective inhibition. According to institutional practice and literature sources, switching the treatment to ticlopidin is safe and effective in more that two-thirds of cases [25]. Increasing the load dose of clopidogrel is also effective, but still there are no data about the ongoing medication management. Moreover there are metabolic individual variations in cytochrome P-450 genes leading to the lower plasma concentrations of active drug metabolite. Prasugrel is a novel thienopyridine with very potent platelet inhibition, which has been recently investigated in acute coronary syndromes [26]. But still there remains a crucial issue that needs further investigation - absence of the prospective randomized data, when almost all the literature data are clinically driven and retrospective with no data derived from large trials suggesting guiding the antiplatelet therapy according to any platelet monitoring results.

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