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Case Report

Non-traumatic splenic rupture on dual antiplatelet therapy with aspirin and ticagrelor after stenting for acute coronary syndrome

Elisa Grifoni (MD)[a,*], Rita Paniccia (BSc)[a], Betti Giusti (BSc)[a], Elena Sticchi (BSc)[a], Luigi Padeletti (MD)[a], Claudio Cavallini (MD)[b], Rossella Marcucci (MD, PhD)[a]

[a] Department and Experimental and Clinical Medicine, University of Florence, Florence, Italy
[b] Division of Cardiology, S.Maria della Misericordia Hospital, Perugia, Italy

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ABSTRACT

We report a case of non-traumatic splenic rupture in a 57-year-old man on dual antiplatelet therapy (DAPT) with aspirin and ticagrelor, seven months after percutaneous coronary intervention and drug-eluting stent implantation for non-ST elevation myocardial infarction. No splenic abnormalities were found at histopathological analysis after splenectomy, and no history of recent trauma was reported. Once restarted, DAPT after splenectomy, assessment of platelet function was performed by light transmittance aggregometry, showing a profound inhibition of platelet function by adenosine diphosphate, arachidonic acid, and collagen. Taking into account the bleeding risk associated with low on-treatment platelet reactivity, and to switch the patient from ticagrelor to a less potent P2Y12 inhibitor such as clopidogrel, cytochrome P450, genetic polymorphisms accounting for clopidogrel response variability were analyzed. The polymorphisms associated with lower response (CYP2C19*2, CYP2C19*3) were absent. Therefore, ticagrelor was withdrawn, and DAPT was continued with aspirin and clopidogrel. Rupture of the spleen may occur in the absence of major trauma or previous splenic diseases, and could be a complication of antithrombotic treatments. Moreover, low on-treatment platelet reactivity during DAPT is emerging as a possible risk factor for bleeding complications, so underlining the usefulness of assessing platelet function in special conditions to ensure that the patient receives the best tailored antiplatelet therapy.

<**Learning objective:** Non-traumatic splenic rupture is a rare event, and is more often associated with pre-existing splenic abnormalities. However, it may be also a complication of medical treatments, especially with antithrombotic drugs. Low on-treatment platelet reactivity is emerging as a possible risk factor for bleeding complications; therefore, assessing platelet function in special conditions could be useful to ensure the patient receives the best-tailored antiplatelet therapy.>

Introduction

Rupture of the spleen is relatively common, both immediately and delayed, after abdominal trauma, whereas non-traumatic splenic rupture is a rare event, and is more often associated with pathological pre-existing splenic abnormalities. Among these, infarction due to cardiac thromboembolism, infectious (i.e. malaria, mononucleosis), inflammatory (i.e. immuno-rheumatologic), and infiltrative (i.e. amyloidosis, hematologic lymphoproliferative, and myeloproliferative neoplasms) diseases have been reported in the literature as the most frequent causes. However, cases of splenic rupture in the absence of trauma or pathological pre-existing conditions, even less frequent, have also been reported. A recent review of the literature showed an association with medical procedures, such as colonoscopy, and ongoing medical treatment with antithrombotic agents, mainly anticoagulants and thrombolytic drugs, but also two cases during antiplatelet therapy with ticlopidine [1–3].

Here, we report a case of non-traumatic rupture of the spleen in a 57-year-old man on dual antiplatelet therapy (DAPT) with aspirin and ticagrelor after percutaneous coronary intervention (PCI) and new generation drug-eluting stent (DES) implantation for non-ST elevation myocardial infarction.

* Corresponding author at: Center for Atherothrombotic Diseases – AOU Careggi, Department and Experimental and Clinical Medicine, University of Florence, Largo Brambilla, 3 – 50134 Florence, Italy. Tel.: +39 055 7949420; fax: +39 055 7949418.
E-mail address: elisa.grifoni@unifi.it (E. Grifoni).

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Case report

A 57-year-old man underwent PCI and new generation DES implantation for non-ST elevation myocardial infarction with angiographic demonstration of two-vessel coronary disease (March 2014). DAPT with aspirin 100 mg once daily and ticagrelor 90 mg twice daily had been started soon after myocardial revascularization, and initially planned to be continued for one year. Seven months after the event, the patient came to medical attention for sudden onset of abdominal pain and hypotension. An abdomen computed tomography showed hemoperitoneum due to splenic rupture. Urgent splenectomy was performed. No signs of splenic infarction or other abnormalities (i.e. micro-aneurysms, inflammatory or infiltrative disorders) were found at histopathological analysis of surgical specimen. No history of recent abdominal trauma had been reported; neither clinical or biohumoral signs suggesting infectious or auto-immune diseases were detected. Laboratory examination showed no significant drop in hemoglobin values, and also showed an increased white blood cell and platelet count ($17.3 \times 10^9\,L^{-1}$ and $1.222 \times 10^9\,L^{-1}$, respectively), as expected after splenectomy. Antiplatelet therapy, with aspirin soon after discharge, together with ticagrelor 15 days later, was restarted. After 10 days, an assessment of platelet function was performed by light transmittance aggregometry (LTA) on platelet-rich plasma (PRP) with an APACT 4004 aggregometer (Axiom, Burstädt, Germany) [4]. This test showed a profound inhibition of platelet function by adenosine diphosphate (ADP) 10 μM, arachidonic acid 1 mM, and collagen 2 μg/mL (LTA 14%, 11%, and 4%, respectively) (Fig. 1). To avoid confounding results due to high platelet count (as normal response after splenectomy), LTA test was repeated with different dilutions of PRP samples, obtaining similar results. Platelet count at the time of the first analysis was $1.247 \times 10^9\,L^{-1}$. Platelet aggregation on the undiluted, and diluted samples with a platelet count of $800 \times 10^9\,L^{-1}$ and $600 \times 10^9\,L^{-1}$ (which is the maximal platelet count recommended for the APACT 4004 light transmittance aggregometer), respectively, are reported in Fig. 2 [5–7]. Taking into account the bleeding risk associated with low on-treatment platelet reactivity and in order to switch the patient from ticagrelor to a less potent P2Y12 inhibitor such as clopidogrel, genetic polymorphisms accounting for clopidogrel response variability were analyzed. Cytochrome P450 polymorphisms associated with a lower response to clopidogrel administration (CYP2C19*2 and CYP2C19*3 alleles) were absent, whereas homozygous CYP2C19*17 polymorphism, which is on the contrary associated with a higher response, was detected [8]. Moreover, no acquired

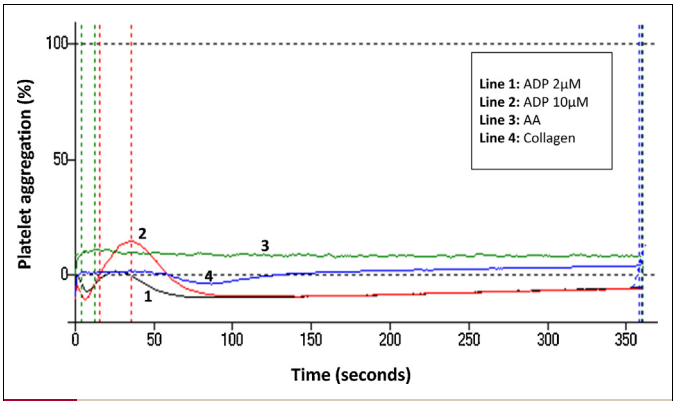

Fig. 1. **Platelet aggregation on light transmittance aggregometry** induced by adenosine diphosphate (ADP) 10 μM, arachidonic acid (AA) 1 mM, and collagen 2 μg/mL after restarting dual antiplatelet therapy with aspirin and ticagrelor.

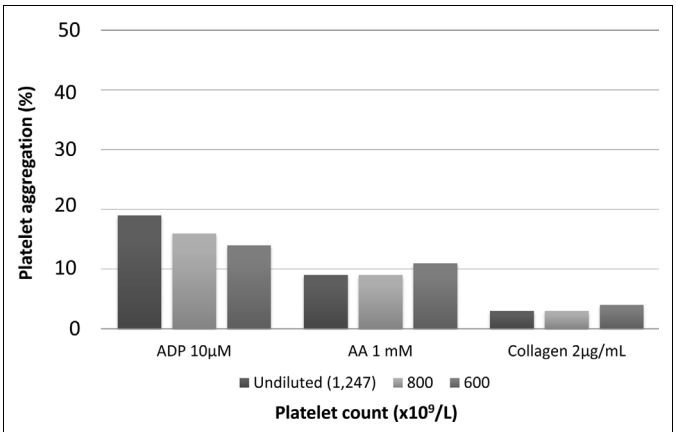

Fig. 2. **Effect of dilution of platelet-rich plasma samples on light transmittance aggregometry** induced by adenosine diphosphate (ADP) 10 μM, arachidonic acid (AA) 1 mM, and collagen 2 μg/mL.

clinical determinants of lower response to clopidogrel, such as older age, diabetes, renal impairment, or heart failure, were present in our patient. Therefore, taking into account both the spontaneous nature of bleeding and laboratory test results, and time elapsed from PCI and stent implantation (more than 6 months) together with the use of less thrombogenic new generation DES, a decision was made to stop ticagrelor treatment and continue DAPT with aspirin 100 mg and clopidogrel 75 mg once daily. Fifteen days after starting clopidogrel, the percentage of platelet aggregation on LTA, with a platelet count of $608 \times 10^9\,L^{-1}$, was 35%, 12%, and 12% by ADP 10 μM, arachidonic acid 1 mM, and collagen 2 μg/mL, respectively. No clinical, instrumental, or laboratory signs raising suspicion of restenosis or stent thrombosis after ticagrelor withdrawal were present. After two months of DAPT with aspirin and clopidogrel, the patient remained asymptomatic, hemoglobin values were stable, and abdomen computed tomography did not show any pathological finding.

Discussion

Non-traumatic splenic rupture is a rare and life-threatening cause of intraperitoneal hemorrhage, and is more often associated with pre-existing splenic abnormalities. Among rare cases of splenic rupture in the absence of trauma or pathological pre-existing conditions, an association with ongoing medical treatment with antithrombotic agents has also been reported [1–3]. To the best of our knowledge, our case is the first description of splenic rupture during DAPT with aspirin and ticagrelor. Neither recent traumatic abdominal injury had occurred, nor history of infectious or auto-immune diseases had been reported in our patient. Moreover, no inflammatory or infiltrative abnormalities of the spleen were documented. DAPT was the only risk factor associated with potential bleeding complications. The profound inhibition of platelet function documented by LTA after restarting treatment with aspirin and ticagrelor might have contributed to the development of a splenic hematoma and consequent rupture of the spleen. Indeed, there is a growing body of evidence that low on-treatment platelet reactivity, induced by ADP and collagen, during antiplatelet treatment with P2Y12 inhibitors is associated with a higher risk of bleeding [9,10]. It has been postulated that there is a therapeutic window for P2Y12 receptor blockers, thus indicating that high on-treatment platelet reactivity is associated with thrombotic events, whereas low on-treatment platelet reactivity is associated with bleeding complications [10].

In conclusion, our case report underlines that rupture of the spleen may occur even in the absence of major trauma or

previously diagnosed splenic diseases, and could be a complication of medical treatments, especially with antithrombotic drugs. Moreover, low on-treatment platelet reactivity during DAPT is emerging as a possible risk factor for bleeding complications in these patients, so underlining the usefulness of assessing platelet function in special conditions, in order to ensure the patient receives the best tailored antiplatelet therapy.

Conflict of interest

Dr Marcucci reported receiving honoraria for lectures from Astra Zeneca, Bayer, Eli Lilly, Merck Sharp Dohme, and Pfizer. No other disclosures were reported.

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