

Case report**Elevated factor VIII Case report: A complicating factor for acute Coronary Syndrome**Octavio Jiménez Melo^{*} José Linares Vicente^{*} Pablo Revilla Martí^{*} Antonela Lukic

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Abstract

Background: Most of the primary percutaneous coronary interventions (PPCI) for ST-elevation myocardial infarction (STEMI) in young patients are not associated with major complications. However, in patients with complications such as hyperacute stent thrombosis or lack of response to anticoagulant therapy, other underlying causes such as thrombophilia must be suspected.

Case summary: A 51-year-old male patient with cardiovascular risk factors who presented with chest pain and Killip class II anterior STEMI. PPCI time was >120 minutes and fibrinolytic strategy failed. He was switched to rescue PCI. Cardiac catheterization showed atherothrombotic occlusion in the proximal left anterior descending artery. PCI was performed with balloon angioplasty and 2 overlapping drug-eluting stents were implanted. Despite administration of 10,000 IU of unfractionated heparin + 100 mg of enoxaparin in a 65-kg patient, the activated clotting time (ACT) did not increase above 250. In the last injections there was an image of repletion contrast defect in the proximal segment of the stent with thrombus material that suggested non-occlusive hyperacute stent thrombosis. A switch to prasugrel and abciximab perfusion was performed. During his hospital stay, a coagulopathy workup was performed, which evidenced elevated factor VIII; the rest of the results were normal.

Discussion: The presence of thrombophilic disorders such as elevated factor VIII in patients undergoing PCI increases the risk of complications during the procedure. In young patients undergoing PCI, thrombophilia should be suspected as a cause of complications and a full study should be performed.

Key Words: acute coronary syndrome; factor VIII; coagulation cascade; case report.

Introduction

Atherothrombosis is the main cause of coronary syndrome, due to the presence of classic cardiovascular risk factors. In some patients, other factors can be responsible for arterial or venous thrombosis. The presence of other thrombophilic risk factors such as high homocysteine, Factor VIII (FVIII), lupus anticoagulant and genetic polymor-

phisms of hemostatic factors (Factor II and Factor V Leiden) should be suspected as responsible or adjuvant mechanism (1,2,3). FVIII is an essential cofactor in the coagulation cascade; FVIII overexpression can trigger thrombotic disorders and complicate acute coronary syndrome (ACS).

Case presentation

A 51-year-old male patient experienced sudden-onset chest pain with vaso-vegetative symptoms at 12:30 h. He was ex-smoker and had other cardiovascular risk factors, including hypertension and dyslipidemia. He had history of psoriatic arthritis under treatment with methotrexate and his sister suffered a stroke when she was 60 years old. The first electrocardiogram showed sinus rhythm with Q wave in V2-V5 and ST elevation in V1-V6-DI-avL (Figure 1). PPCI time was >120 minutes and fibrinolytic strategy (7,000 IU tenecteplase) was chosen. Acetylsalicylic acid (ASA) 250 mg + clopidogrel 300 mg + enoxaparin (30 mg intravenous bolus and 70 mg subcutaneous bolus) + nitroglycerine perfusion were administered. Fibrinolysis failed. He was switched to rescue PCI. Physical examination showed normal blood pressure of 100/60 mmHg, a regular heart rate of 100 bpm and crackles in both lung fields. Coronary angiography showed proximal left anterior descending artery atherothrombotic occlusion and a lesions in the circumflex and right coronary artery (non-infarct related vessel). PCI was performed with balloon angioplasty and 2 overlapping drug-eluting stents were implanted with good angiography outcome (Figure 2). In the last injections, there was an image of the haziness or repletion contrast defect in the proximal segment of the stent, which was consistent with thrombus material; the ACT was no greater than 250 despite the administration of 10,000 IU of unfractionated heparin, weighing 65 kg, and after 100 mg of enoxaparin (Figure 3). Stent boost confirmed the absence of images of stent fracture. Balloon angioplasty (3.0/12 mm) reduced thrombotic burden in the vessel with final TIMI flow 3. Based on the angiographic findings, a switch to prasugrel was made. Initial medical treatment was decided for the non-infarct related vessel.

He was admitted to the coronary unit under treatment with ASA + prasugrel + continuous perfusion of unfractionated heparin + abciximab. Necrosis markers were CPK 9283 U/L, CKMB 821 U/L and high sensitivity troponin >10,000 ng/L.

Favorable evolution in Cardiology unit. He started treatment with

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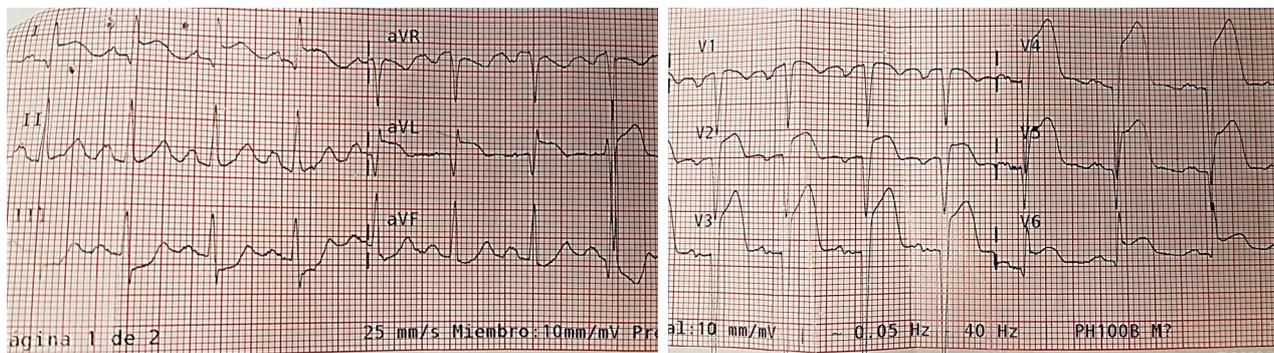


Figure 1: STEMI diagnosis. The electrocardiogram showed sinus rhythm with Q wave in V2-V5 and ST elevation in V1-V6-DI-avL.

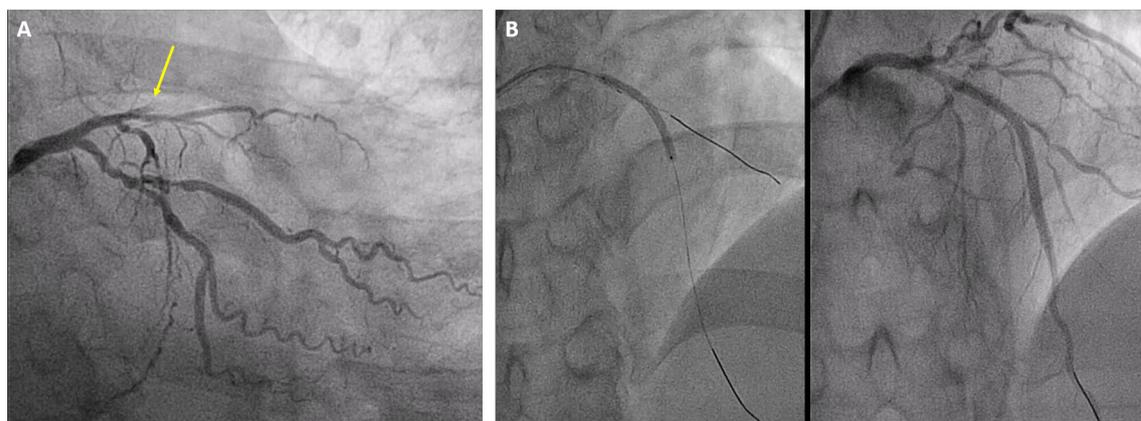


Figure 2: Coronary angiography. (A): proximal left anterior descending artery atherothrombotic occlusion. (B) PCI result: balloon angioplasty and 2 overlapping drug-eluting stents (2.75/30 mm and 2.5/12mm).



Figure 3: Repletion contrast defect in the proximal segment of the stent with thrombus material that suggested non-occlusive hyperacute stent thrombosis. Lack of effect of anticoagulant agents (ACT < 250).

Pro-coagulant factor	Values
Factor VIII*	205.6% (Reference value 60-120)
Homocysteine	Negative
FII mutation (prothromb.)	Negative
FV Leiden mutation	Negative
Antithrombin	95% (Reference value: 80-120)
Lupus anticoagulant	Normal
ANA	Negative
ANCAs	Negative

* The one-stage FVIII clotting assay was performed on an ACL-TOP 750 coagulometer (Instrumental Laboratory, Bedford, MA, USA) using Hemosil SynthAsil aPTT reagents (Instrumentation Laboratory, IL) as activator and phospholipid source, and Hemosil FactorVIII deficient plasma (IL).

Figure 4: Thrombophilia tests.

of the thrombophilia tests were normal. There were not more ischemic or hemorrhagic events during the follow-up.

Discussion

In case of hemorrhage or vascular damage, the natural repair mechanism is the production of fibrin to form a repair matrix with the platelets. Factor IXa requires Factor VIIIa to activate factor X to be able to continue the coagulation cascade until the formation of fibrin (Figure 5). Therefore, FVIII plays an essential role in the clotting process. This has been demonstrated in patients with hemophilia A, in whom FVIII deficiency results in significant bleeding diathesis (4). The relationship between factor VIII and arterial thrombosis may be based on the

angiotensin-converting-enzyme inhibitors, beta-blocker, and mineralocorticoid antagonist. Persistent elevation of anteroseptal ST in Q-wave. Echocardiography showed a mild systolic dysfunction with apex and anteroseptal akinesia and apical wall thrombus. For this reason it was decided to initiate oral anticoagulation and switch to clopidogrel (clopidogrel resistance was ruled out).

After 7 days, laboratory tests showed high FVIII of 205% that could justify resistance to unfractionated heparin (Figure 4). He was discharged with ASA, clopidogrel and warfarin/acenocoumarol, due to presence of left ventricular thrombus. During the follow-up, the rest

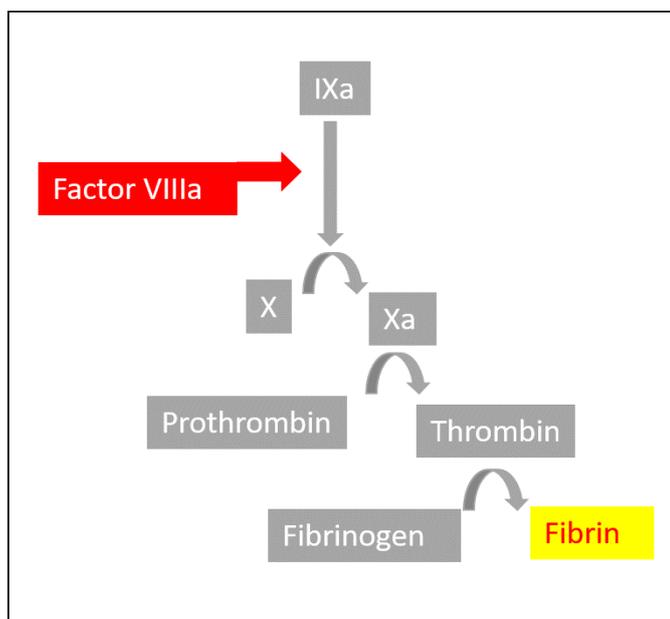


Figure 5: FVIII. Coagulation cascade.

combination of increased fibrin formation and increased platelet adhesion/aggregation at sites of arterial wall damage (5, 6).

The prevalence of elevated FVIII is 11% in healthy control subjects and high levels are described in up to 25% of patients with thrombosis. Factor VIII levels ≥ 150 IU/dL account for 16% of all venous thrombotic events, whereas factor VIII levels > 123 IU/dL explain 4% of all arterial events (5, 7). The increased thrombotic risk associated with factor concentration would be a “continuous function”, so the cut-off points would be set somewhat arbitrarily. High factor VIII levels are the result of a combination of genetic and acquired factors. The high number of preanalytical variables and clinical conditions that can influence the outcome of a specific measurement of these levels should be taken in consideration (5, 8). The values of FVIII can vary in acute situations, inflammatory conditions, obesity, diabetes, insulin, liver disease, malignancy, hyperthyroidism and even based on ethnicity. Individuals with blood group non-O have higher levels of factor VIII than do those with blood group O (5, 9, 10, 11).

Some particular and infrequent aspects were shown in our case and led the authors to suspect basal thrombophilia, such as the lack of anticoagulant effect in spite of high doses of heparin and the presence of a non-occlusive acute stent thrombosis (12). After 7 days, laboratory tests showed high FVIII of 205%.

Patients with a venous thrombosis diagnosis and an elevated FVIII, chronic oral anticoagulation is known to prevent recurrences (13). However, benefits of chronic oral anticoagulation in the context of arterial thrombosis is not well established. Some case reports describe patients presenting with an ACS without classic cardiovascular risk factors but elevated FVIII, in whom chronic oral anticoagulation is started (14).

Limitations: it is highly recommends intracoronary imaging in the setting of stent complications, but, one of the key limitations is the additional time required for imaging (15). This case was very prolonged, and the lack of effect of the anticoagulation justified the termination of the procedure to avoid further complications such as catheter thrombosis. Another problem was the timing of the measurement of factor VIII, because many variables such as acute thrombotic episode, antiaggregat

treatment and many other variables can modify the values.

Our patient was under treatment with ASA and prasugrel. However, there are still too many questions to be answered about the timing of factor VIII measurement (5).

Another factor to consider in order to avoid thrombotic complications is the selection of appropriate antiplatelet therapy (16). In the context of STEMI, the different therapeutic window of clopidogrel (2-4 hours) and ticagrelor-prasugrel (30 minutes) may contribute to thrombotic complications (17). Cangrelor is a direct and reversible intravenous P2Y12 inhibitor that blocks ADP. One of its advantages is the rapid onset of the effect in only 2 minutes. It also provides a consistent pharmacological effect independently of clinical presentation (acute or chronic scenario) or clinical profiles such as gender, age, renal function (18). Therefore, cangrelor could be considered a more suitable P2Y12 inhibitor in certain clinical scenarios, for instance when a patient suffer acute stent thrombosis.

Conclusions

The presence of thrombophilic disorders such as elevated factor VIII in patients undergoing PCI involves a greater risk of complications during the procedure. In young patients undergoing PCI, thrombophilia should be suspected as a cause of complications and a full work-up should be performed to establish the cause of the complications. Establishing thrombophilia helps prevent future complications when scheduling new PCI.

Conflict of interest: All authors have no conflicts of interests or disclosures to report.

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