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Case report

Unexplained pulmonary embolism post SARS-CoV2 pneumonia in a patient with MYH9-related disease: a case report

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Abstract. This report describes the case of a man affected by Myosin Heavy Chain 9 (MYH9)-related platelet disorder, with a recent history of SARS-CoV-2 pneumonia, who developed pulmonary embolism (PE). At the admittance the patient presented a marked thrombocytopenia. The rotational thromboelastometry (ROTEM) showed a reduction in maximum clot firmness. The CT scan showed a lobar PE while and no sign of superficial or deep venous thrombosis was found. Given the contraindication of anticoagulant therapy due to severe thrombocytopenia, after collegial evaluation of the case, an inferior vena cava filter was applied. The patient was discharged after 5 days of hospitalization, and fondaparinux 2.5 mg subcutaneously was prescribed for two months. Could MYH9 mutation contribute to thrombotic predisposition? Or rather the endothelial dysfunction induced by SARS-CoV-2 infection? The report presents a dissertation on the possible causes for the PE and describes the therapeutic strategy adopted. (www.actabiomedica.it)

Key words: MYH9-related disease, macrothrombocytopenia, SARS-CoV-2 pneumonia, pulmonary embolism, ROTEM

Introduction

Myosin Heavy Chain 9 (MYH9)-related platelet disorders are among rare forms of hereditary thrombocytopenia. Mutations in the MYH9 gene lead to macrothrombocytopenia, and cytoplasmic inclusion bodies within leukocytes. Renal failure, hearing loss and presenile cataracts are among the clinical manifestations of this disorder [1]. Acute pulmonary embolism (PE) is a significant cause of morbidity, representing the third most common cause of cardiovascular death among inpatients in the Western countries following acute myocardial infarction and stroke. The most common risk factor for PE is a history of deep vein thrombosis, but also malignancies, recent surgery, and a history of hypercoagulability augment the risk of this disease. The pathogenesis is described by the Virchow's Triad: blood stasis, hypercoagulability, and endothelial vessel wall injury [2]. More recently, an important cause of PE is acute COVID-19: among patients suffering the severe form of this disease the prevalence of acute thrombotic events is high [3]. To date, this is the first case report describing a patient affected by MYH9-related platelet disorder who developed PE, and the treatment strategy adopted given a condition of severe thrombocytopenia.

Case report

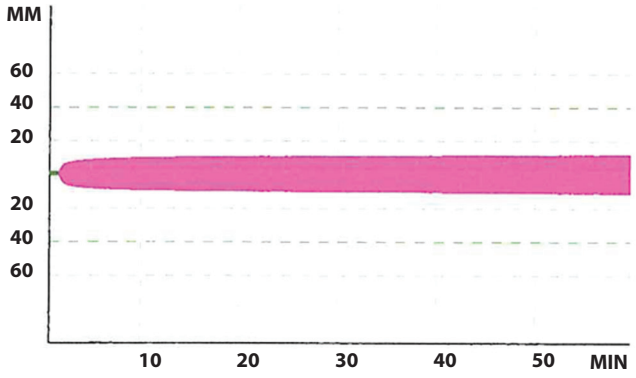
A 66-year-old Caucasian man was admitted to the Emergency Medicine ward for pulmonary embolism, which was detected during an outpatient CT

control three weeks after his recent hospital admission for SARS-CoV2 pneumonia. On the physical examination at the entrance the patient was alert, cooperating, with no apparent signs of segmental neurological deficits. Cardiac activity was rhythmic, with free pauses. Vesicular murmur was present throughout all pulmonary lobi, with no wheezing, rhonchi nor crackles. The abdomen was soft, nontender, non-distended, with no pain, no hepatosplenomegaly, and normal bowel sounds. No subcutaneous edema. Vital parameters: cardiac frequency 85 bpm, arterial pressure 135/80 mmHg, SpO_2 95%, apyretic. Blood cell count at the admittance showed: leukocytes 4.21 $x10^3$/mmc, erythrocytes 4.88 $x10^6$/mmc, hemoglobin 13.9 g/dl, hematocrit 43,8%, Mean Corpuscular Volume (MCV) 90 fl, Mean Corpuscular Hemoglobin (MCH) 28.5 pg, Mean Corpuscular Hemoglobin Concentration (MCHC) 31.7 g/dl, Red blood cell Distribution Width-Variation Coefficient (RDW-CV) 15.9%, platelets 25 $x10^3$/mmc. Moreover, lab tests showed: prothrombin activity 106%, International Normalized Ratio (INR) 0.90, Activated Partial Thromboplastin Time (APTT) 24 sec., ratio 0.78, fibrinogen 352 mg/dl, D-dimer 2,272 ng/ml, creatinine 0.86 mg/dl, troponin I hs 13 ng/l, Brain Natriuretic Peptide (BNP) 20 pg/ml. Viscoelastic hemostatic assay was performed via rotational thromboelastometry (ROTEM® Sigma, Tem Innovations GmbH, Munich, Germany) as showed in Figure 1, and highlighted: Coagulation Time $(CT)_{EXTEM}$ 74 sec. (reference values – RV – 50-80 sec.), clot amplitude 5 min after CT (A5) $_{EXTEM}$ 24 mm (RV 32-52 mm), Maximum Clot Firmness $(MCF)_{EXTEM}$ 47 mm (RV 56-72 mm), CT_{INTEM} 163 sec. (RV 161-204 seconds), MCF_{INTEM} 45 mm (RV 51-69 mm), MCF_{FIBTEM} 11 mm (RV 6-21 mm). The CT scan showed multiple thromboembolic filling defects affecting branches of both pulmonary arteries: on the right involving the upper lobar, intermediate and lower lobar branches and their segmental-subsegmentary branches, and on the left involving the segmental-subsegmentary tributary branches for the basal pyramid. The venous echocolordoppler of the lower limbs showed no signs of deep or superficial vein thrombosis bilaterally. The patient presented a recent history of SARS-CoV2 pneumonia which required the hospitalization (discharged three weeks before the detection of PE). Moreover, he was affected by the MYH9-related platelet disorder (first misdiagnosed in 1987 as a Bernard-Soulier syndrome) with chronic kidney disease, which required a renal transplant in 2010, macrothrombocytopenia, hearing loss and cataracts. After a collegial evaluation of the case, it was decided to treat the PE placing and Inferior Vena Cava (IVC) filter. Therefore, on ultrasound guide and under X-ray control, through percutaneous access into the right common femoral vein, the IVC filter was placed in the infra-renal inferior vena cava. During the hospitalization the patient underwent a gradual improvement of symptoms in the absence of acute events. Laboratory tests at discharge (after 5 days-hospitalization) showed: leukocytes 4.88 $x10^3$/mmc, erythrocytes 4.64 $x10^6$/mmc, hemoglobin 13,1 g/dl, hematocrit 40%, MCV 86 fl, MCH 28.2 pg, MCHC 32,8 g/dl, RDW-CV 14,1%, platelets 39 $x10^3$/mmc, creatinine 0,75 mg/dl. Fondaparinux 2.5 mg 1 ampoule subcutaneously was prescribed for two months. The subject was referred for outpatient follow-up and to evaluate possible removal of the IVC filter.

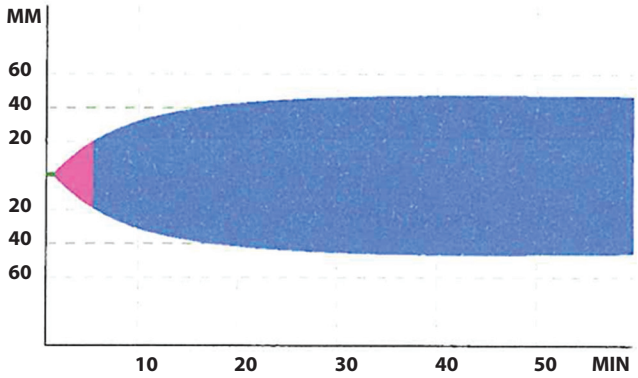
Discussion

First described in 1909, the MYH9-related disorders are a group of rare hereditary syndromes caused by mutations in the MYH9 gene, which cause alterations of the protein non-muscle myosin IIA, a mechanoenzyme involved in cell motility, leading to the formation of giant platelets. According to the type of mutation, clinical features of these disorders include macrothrombocytopenia, leukocytes inclusion bodies, hearing loss, nephritis and cataract. Despite the number of platelets (from 30,000/mmc to 100,000/mmc), the degree of bleeding tendency, renal impairment and the onset of cataracts and hearing loss, vary among individuals. Bruising and hematomas are very frequent but major bleeding episodes are rare. The prevalence of MYH9-related disorders is unknown and only a few hundreds of families are known. An important risk for these subjects is the inappropriate treatment due to misdiagnosis. In fact, among the macrothrombocytopenias to be considered in the differential diagnosis of MYH9-related disorders, there are five rare

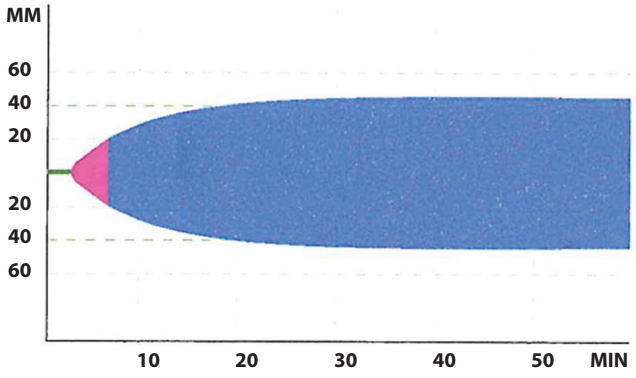
Figure 1. Viscoelastic hemostatic assay via rotational thromboelastometry (ROTEM® Sigma, Tem Innovations GmbH, Munich, Germany)



FIBTEM C	Value	Reference
CT	72 sec	46-84 sec
CFT		
A5	9 mm	5-20 mm
A10	10 mm	6-21 mm
A20	11 mm	6-21 mm
A30	11 mm	6-21 mm
MCF	11 mm	6-21 mm
LI30	100 %	91-100 %
LI45	100 %	89-100 %
LI60	100 %	89-100 %

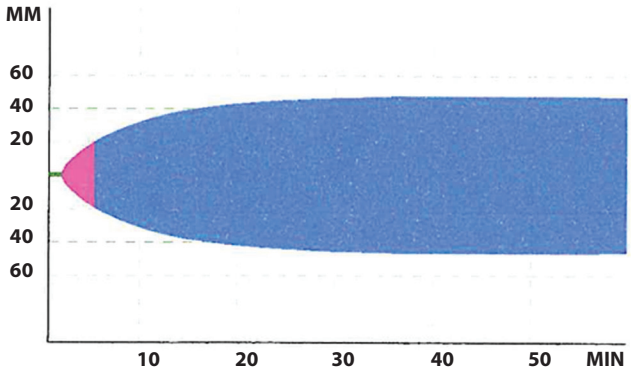


EXTEM C	Value	Reference
CT	74 sec	50-80 sec
CFT	229 sec	46-149 sec
A5	24 mm	32-52 mm
A10	34 mm	43-63 mm
A20	43 mm	52-70 mm
A30	46 mm	52-72 mm
MCF	47 mm	56-72 mm
LI30	100 %	
LI45	100 %	98-100 %
LI60	99 %	94-100 %



INTEM C	Value	Reference
CT	163 sec	161-204 sec
CFT	227 sec	62-130 sec
A5	24 mm	33-52 mm
A10	34 mm	43-62 mm
A20	42 mm	50-68 mm
A30	45 mm	51-69 mm
MCF	45 mm	51-69 mm
LI30	100 %	98-100 %
LI45	100 %	92-100 %
LI60	98 %	87-100 %

(*Continued*)



APTEM C	Value	Reference
CT	100 sec	41-80 sec
CFT	206 sec	62-184 sec
A5	25 mm	28-50 mm
A10	35 mm	39-61 mm
A20	44 mm	48-68 mm
A30	46 mm	51-71 mm
MCF	47 mm	52-77 mm
LI30	100%	
LI45	100 %	98-100 %
LI60	99 %	93-100 %

Abbreviations: FIBTEM (extrinsically activated test with tissue factor, the platelet inhibitor cytochalasin D and the heparin inhibitor polybrene); CT: Coagulation Time (time until the formed clot reaches a clot firmness of 2 mm); CFT: Clot Formation Time (time between 2 mm and 20 mm clot firmness); A5: clot amplitude 5 min after CT; A10: clot amplitude 10 min after CT; A20: clot amplitude 20 min after CT; A30: clot amplitude 30 min after CT; MCF: Maximum Clot Firmness; LI30: Lysis Index 30 (residual clot firmness in percentage of MCF 30 min after CT); LI60: Lysis Index 60 (residual clot firmness in percentage of MCF 60 min after CT); EXTEM (extrinsically activated assay with tissue factor and the heparin inhibitor polybrene); INTEM (intrinsically activated test using ellagic acid); APTEM (extrinsically activated test with tissue factor, blocking hyperfibrinolysis by tranexamic acid and the heparin inhibitor polybrene).

disorders. Firstly, the chronic autoimmune thrombocytopenia, which is not hereditary, less than 10% of platelets are giant, presents platelet glycoprotein-specific autoantibodies, and responds to intravenous IgG. Secondly the Bernard-Soulier syndrome (BSS), an autosomal recessive disorder, caused by reduced or absent expression of glycoprotein Ib-IX-V receptor complex. The case described in this report was at first diagnosed with BBS. Indeed, after analyzing the distribution of the heavy chains of non-muscle myosin IIA in the granulocytes of the peripheral blood smear through indirect immunofluorescence technique, the observed picture was indicative of the presence of mutation in the MYH9 gene. In third instance the MYH9-related disorder may be misdiagnosed for the Paris-Trousseau syndrome, caused by the heterozygous deletion of chromosome 11q23, and characterized by giant platelets containing giant alpha-granules, mental retardation, facial and cardiac abnormalities. Finally, other possible differential diagnoses are the X-linked macrothrombocytopenia, caused by mutation in the GATA-1 gene Xp11-12, and Gray platelet syndrome, an autosomal recessive disorder [1].

The occurrence of a thrombotic diathesis in a patient with MYH9-related disorder and severe thrombocytopenia deserves some comments. Firstly, the case hereby described presented no sign of deep nor superficial venous thrombosis. Secondly, of note, the patient underwent recently a SARS-CoV-2 pneumonia and was discharged from the COVID ward just three weeks before the detection of the PE without anti-thrombotic prophylaxis. In third instance, besides the routine coagulation tests, which focus only on either the extrinsic or the intrinsic coagulation pathway and are performed using blood plasma, coagulation was investigated also via rotational thromboelastometry using the viscoelastic hemostatic assay ROTEM® Sigma (Tem Innovations GmbH, Munich, Germany). Whole blood is inserted into a pre-warmed to 37°C cup. Then, a pin that is connected to an optical detector is immersed in the blood. When the measurements start, the pin initiate to move at a defined angle. As coagulation proceeds, a blood clot is formed and oscillation becomes restricted; this change is detected by the respective systems and a digital output is generated by the integrated software, which provides a graphic presentation of clot formation and lysis. The ROTEM measurements are run for 60 minutes and the following specific tests are performed: EXTEM (extrinsically activated assay with tissue factor and the heparin inhibitor polybrene); INTEM (intrinsically activated test using ellagic acid); FIBTEM

(extrinsically activated test with tissue factor, the platelet inhibitor cytochalasin D and the heparin inhibitor polybrene); APTEM (extrinsically activated test with tissue factor, blocking hyperfibrinolysis by tranexamic acid and the heparin inhibitor polybrene) and HEPTEM (intrinsically activated test using ellagic acid and inactivating heparin by heparinase) measurements. These tests are contained in two cartridges and the reference intervals have been identified through several studies [4]. The data provided by this device are used to optimize blood management in trauma and surgical bleeding patients [4-6]. Given the high prevalence of thrombotic events in severely ill COVID-19 patients, a recent study aimed to test whether ROTEM at admission was associated to hypercoagulopathy and a predictor of COVID-19 severity. The authors observed that the variables MCF_{EXTEM} and MCF_{FIBTEM} presented significantly higher values in COVID-19 patients compared with healthy controls ($p < 0.001$) and higher in severely ill patients compared with inpatients at regular wards ($p < 0.05$) [7]. In contrast to the study's data, this case showed a reduction of the MCF_{EXTEM} and MCF_{INTEM}, and a reduced clot amplitude 5 min after clotting time. Nevertheless, lobar pulmonary embolism was developed. It would be of interest to investigate the role of these alterations in the MYH9-related disorder. Given the absence of DVT, given the coagulation parameters in the normal range, what could be the leading cause of the PE? Could the endothelial dysfunction (induced by SARS-CoV-2 infection) result in a pro-thrombotic state of the vessel walls leading to microthrombi formation despite the marked thrombocytopenia in this patient? Finally, it is interesting to observe that, despite the reduced platelet counts, subjects with MYH9-related disorders are not protected from thrombosis. A case of unexplained recurrent venous thrombosis in a patient with MYH9 related disease has been reported in literature [8]. Could the MYH9 mutation contribute to thrombotic predisposition? Given that the potential underlying mechanisms remains unknown, could we hypothesize that this mutation might induce endothelial cell dysfunction, or result in platelet hyperactivity. Possibly the answer lays in a synergistic activity exerted by the alterations induced by SARS-CoV-2 infection and the MYH9 mutation.

According to the ESC Guidelines, therapeutic anticoagulation for ≥3 months is recommended for all patients. Non-vitamin K antagonist oral anticoagulants (NOACs, such as apixaban, dabigatran, rivaroxaban, and edoxaban) are recommended as the first choice for anticoagulation treatment in a patient eligible; vitamin K antagonists (VKAs) are an alternative to NOACs [9]. In this case a therapeutic dose of anticoagulants would expose the patient to an excessive bleeding risk. Therefore, after collegial evaluation of the case, given the indication of the ESC Guidelines, it was decided to place an IVC filter and to prescribe fondaparinux 2.5 mg for two months to prevent DPT occurrence.

This report presents some strengths. To our knowledge, it is the first time in literature that a case of PE is described in a subject with MYH9-related disorder. The ROTEM measurement offers interesting insights on the possible causes of the PE. The etiopathogenetic hypotheses hereby formulated, and the therapeutic strategy adopted could be of interest for those who will be dealing similar patients. Moreover, to redact this case study, the CARE Guidelines were followed, thus improving the scientific value of the paper [10]. Nevertheless, it has some limitations. MYH9-related disorders are rare conditions, often misdiagnosed or underreported. At first, the patient was diagnosed a BSS and Alport syndrome. Then, twenty year later, the indirect immunofluorescence revealed a granulocyte alteration compatible with MYH9-related disease which allowed to reach the correct diagnosis. Identifications of large cohorts of patients and long-term follow-up would help to better understand this disease and its pathophysiological characteristics with particular regard to the thrombotic diathesis, thus improving appropriate diagnosis and treatment. Moreover, deepen the knowledge regarding SARS-CoV-2 infection and consequences on the cardiocirculatory system would help to thrombotic events in selected cohort of subjects.

Authors' contribution: VGM had the idea of the manuscript. LT and VGM developed the study design and drafted the manuscript. LT wrote the case report. LT, VGM, CN and AS reviewed, participated to the editing and final drafting of the manuscript and approved the final version of it.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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