Troubleshooting an isolate prolongation of activated partial thromboplastin time in a patient with acute myocardial infarction—a paradigmatic case report

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Abstract: We describe here the case of a 46-year-old man admitted to the emergency department (ED) and diagnosed with a non-ST elevation myocardial infarction. Before referring the patient to the coronary care unit and initiating antiplatelet and anticoagulant therapy, a highly prolonged activated partial thromboplastin time (APTT) was observed among results of laboratory testing. Results of mixing test showed complete correction of APTT, thus ruling out the presence of inhibitors of blood coagulation. On the following day, second line coagulation testing revealed normal activity of all clotting factors except factor XII, the concentration of which was found to be 1.5%. This result was suggestive for a diagnosis of inherited factor XII deficiency, thus highlighting the importance of combining clinical history, symptoms and results of first-line coagulation tests in similar emergency conditions.

Keywords: Myocardial infarction; factor XII; activated partial thromboplastin time (APTT); mixing test; laboratory diagnostics

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Case presentation

A 46-year-old man was admitted to the emergency department (ED) of the University Hospital of Verona (Italy), complaining of chest pain lasting for 1 hour. As for standard practice (1), he underwent testing for evaluation of potential acute myocardial infarction (AMI). The electrocardiogram (ECG) initially revealed minimal alterations of septal repolarization, the cardiac troponin T (cTnT) value was already above the diagnostic threshold at ED admission, and increased further in the following hours (*Table 1*). Echocardiography performed at ED admission revealed left ventricular contractile disturbances with apical and septal akinesia and mild hyperkinesia of basal segments. A final diagnosis of non-ST elevation myocardial infarction (NSTEMI) could hence be established. Patient consent about data treatment was obtained upon patient admission as for routine practice at the University Hospital of Verona.

Before referring the patient to the coronary care unit, additional laboratory tests were requested, the results of which are also shown in *Table 1*. Beside the enhanced values of cTnT, which were obviously attributable to the presence of myocardial ischemic injury (2), an isolate prolongation of the activated partial thromboplastin time (APTT) was the only other clinically significant abnormality. Due to the diagnosis of NSTEMI, the laboratory staff initially attributed the APTT prolongation to administration of heparin, as for standard care of this condition. However, the emergency physician reported that the blood sample had been collected before initiating any type of therapy in the ED, nor had the patient been administered heparin or other anticoagulants prior to ED

Table 1 Laboratory data obtained at ED admission and the day after

Parameter	Time	Value	Reference range
Day of ED admission			
Hemoglobin (g/L)	9:30 PM	161	135–170
Platelet count (×10^9/L)	9:30 PM	250	150–400
Cardiac troponin T (ng/L)	9:30 PM	35	<14
	0:30 AM	573	<14
	5:30 AM	1,431	<14
Creatinine (μmol/L)	9:30 PM	88	53–115
PT	9:30 PM	10.6	9.0–12.9
PT-INR	9:30 PM	0.94	0.82–1.17
APTT (s)	9:30 PM	257.0	24–36
APTT ratio	9:30 PM	8.89	0.80–1.20
APTT mixing test (s)	9:30 PM	30.0	24–36
D-dimer (μg/L)	9:30 PM	202	<500
Fibrinogen (g/L)	9:30 PM	2.19	2.00–4.00
Day after ED admission			
Factor VIII (%)	9:00 AM	124.2	50–150
Factor IX (%)	9:00 AM	101.1	50–150
Factor XI (%)	9:00 AM	99.2	60–130
Factor XII (%)	9:00 AM	1.5	60–130

ED, emergency department; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time.

admission. It was also clearly ascertained that blood was drawn from a peripheral vein, thus excluding potential contamination with heparin from intravenous lines. Owing to the compelling need to timely establish anticoagulant and antiplatelet therapy for the treatment of NSTEMI, but due to the lack of a suggestive clinical history of bleeding and the absence of hemorrhagic symptoms, a mixing test was performed by the laboratory according to current indications (3). Briefly, one volume of patient plasma was mixed with one volume of normal pooled plasma (e.g., 1+1 mL). The mixture was then incubated for 2 hours at 37 ℃, followed by measurement of APTT in both aliquots. The results of the mixing test showed complete correction of the APTT value, thus ruling out the presence of inhibitors of blood coagulation (i.e., excluding heparin or antibodies against coagulation factors) (*Table 1*). On the reliable assumption the APTT prolongation was attributable to a non-clinically significant coagulation abnormality, the patient was then transferred to the coronary care unit and coronary angioplasty was finally performed. On the following day, second line coagulation testing was performed, revealing normal activity of all clotting factors of the intrinsic pathway except for factor XII, the concentration of which was found to be 1.5%. This result was hence suggestive for a final diagnosis of inherited factor XII deficiency (*Table 2*).

Discussion

The potential causes of an isolate APTT prolongation are many and multifaceted, and mostly include congenital or acquired clotting factor deficiencies (i.e., congenital or acquired hemophilia), heparin therapy, lupus anticoagulants and preanalytical errors (e.g., inadequate blood to anticoagulant ratio, contamination with EDTA or heparin during blood drawing) (4). Troubleshooting the underlying problem in urgent settings, when second-line coagulation testing is unavailable, necessitates an accurate collection of clinical history, critical evaluation of presenting symptoms, analysis of specimen quality, combined with results of both APTT and a mixing test. As clearly described in *Table 2*, the three main aspects characterizing this case report were a negative clinical history for bleeding, the lack of hemorrhagic symptoms at ED admission and the complete correction of APTT values after mixing studies. The only clinical condition in which these three aspects are concomitant is a high stage contact factor deficiency, of which factor XII deficiency is most often identified (5).

Indeed, inherited factor XII deficiency is probably the most frequent cause of APTT prolongation in clinical laboratories (6). Due to the virtually irrelevant role of this protein in physiological hemostasis, such inherited deficiencies are typically characterized by variably prolonged APTT values (depending on residual factor activity and reagent sensitivity) and total lack of bleeding tendency even with major surgical procedures or trauma (7). Nevertheless, the former aspect (i.e., the APTT prolongation) may be responsible for major diagnostic dilemmas, especially when the test is performed in patients needing a timely clinical management by means of anticoagulation or surgery and when second-line coagulation testing is unavailable. In such cases, the lack of awareness of this clinically meaningless abnormality may lead to unjustified delays of patient

Table 2 Potential causes of an isolated prolongation of the APTT

Cause	History of bleeding	Hemorrhagic symptoms	Mixing test
Congenital clotting factors deficiencies			
Factor XII deficiency	Usually absent	Absent	Correction
Factor VIII deficiency	Highly suggestive	Present	Correction
Factor IX deficiency	Highly suggestive	Present	Correction
Factor XI deficiency	Suggestive	Variably present	Correction
Acquired haemophilia	Usually absent	Present	No correction
Heparin therapy	Usually absent	Variably present	No correction
Lupus anticoagulant	Usually absent	Absent	No correction

APTT, activated partial thromboplastin time.

treatment.

In addition, factor XII deficiencies in patients such as ours then create ongoing difficulty for management, should heparin therapy be applied, and should this then require monitoring. Given the high baseline APTT, this test is no longer suitable to monitor heparin therapy in these patients, and instead, direct assessments by anti-activated factor X (FXa) tests are required (8). Monitoring issues do not cease there. Given the high baseline APTT, any anticoagulant given to the patient to treat any future event will invalidate any attempt to assess for effects using routine coagulation tests. This will include any future use of the newer direct anticoagulant drugs, such as dabigatran, rivaroxaban, apixaban and edoxaban, which will then only be able to be evaluated using specific anti-activated factor II (FIIa) or anti-FXa tests (9,10).

In conclusion, this case report emphasizes the importance of a strict collaboration between the clinics and the laboratory, wherein many diagnostic challenges such as that presented in this article can be efficiently resolved by combining clinical history, symptoms and results of first-line coagulation tests, thereby facilitating quick resolution of clinical diagnosis and not unduly delaying urgent patient management.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Patient consent about data treatment was obtained upon patient admission as for routine practice at the University Hospital of Verona.

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