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

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.
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 °C, 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).

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

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

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

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
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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None.

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.

References

