Case report

Concomitant ST-elevation myocardial infarction and deep vein thrombosis in a patient with severe factor XII deficiency: case report and review of the literature

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Since its first discovery in 1955, coagulation factor XII (FXII) deficiency was, quite surprisingly, linked with thrombosis instead of haemorrhage; indeed, John Hageman ultimately died from pulmonary embolism.1 After this, several reports have highlighted the association between both arterial and venous thrombosis and FXII deficiency; however, a causal relationship is still questioned. Here, we report the case of a woman with severe factor Hageman deficiency who was presented with concomitant myocardial infarction and deep vein thrombosis.

An 86-year-old woman presented to the Emergency Department because of sudden onset dyspnoea. After initial evaluation, the presence of bilateral femoral vein thrombosis was noted (Figure 1); a computed tomography scan did not reveal pulmonary embolism and was remarkable for the presence of ground-glass bilateral opacities and suspected secondary lesions of the lungs and liver (Figure 2). Electrocardiogram (Figure 3) and cardiac enzymes were consistent with subacute, ST-elevation myocardial infarction (STEMI), and the patient was admitted to Coronary Care Unit. Blood test results at admission are shown in Table 1. Due to the presence of prolonged activated partial thromboplastin time (aPTT), that was interpreted as caused by liver infiltration and insufficiency, the patient was treated with aspirin only and, on fifth day, transferred to our ward for further evaluation.

The patient was a former smoker, with a previous history of pneumonia and penicillin allergy. She reported a traumatic left leg fracture. She was under treatment with levothyroxin for Hashimoto disease, and with folate and vitamin B12 for a previous anaemia. On further questioning, the patient reported a spontaneous abortion when she was 21; her sister has a daughter with ‘haemophilia’. The patient suffered from frequent epistaxis before

![Figure 1. Ultrasound and doppler scan of the left femoral vein showing hypoechoic filling defect, that was proven to be incompressible.](image-url)
puberty; however, neither excessive bleeding nor thrombosis was noted when she fractured her leg. After searching our database, we found that the patient was admitted to our department in December 2000 because of megaloblastic anaemia; blood tests are shown in Table 2. We had discharged her at that time with a diagnosis of severe FXII deficiency (3% activity). On the present occasion, we treated the patient with aspirin and full dose of fondaparinux; as she refused further diagnostic evaluation, we transferred her to a hospice facility.

FXII is a plasma serine protease known to be implied in the so-called extrinsic pathway of coagulation; upon autoactivation after exposure to negatively charged surfaces, activated FXII (FXIIa) generates in turn Factor XI, prekallikrein and C1 esterase; furthermore, it seems to contribute to plasmin generation, thus participating in haemostasis, fibrinolysis, vascular permeability and complement cascades.2 However, its deficiency is not associated with significant bleeding diathesis3 and, in most cases, the condition is discovered by chance in occasion of screening tests. It is less well understood if, and how, FXII deficiency represents a risk factor for both arterial and venous thrombosis of usual or unusual sites. This association is mainly suggested by many case reports,4–19 a large part of which were reported in the era before the discovery of common inherited thrombophilias (i.e. Factor V Leiden or prothrombin G2010 mutation); in more

Table 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal values</th>
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<tbody>
<tr>
<td>aPTT (s)</td>
<td>167</td>
<td>23–34</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>7226</td>
<td>&lt;230</td>
</tr>
<tr>
<td>Creatine kinase, MB (ng/ml)a</td>
<td>67.8</td>
<td>0.0–6.6</td>
</tr>
<tr>
<td>Troponin I (ng/ml)a</td>
<td>10.47</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Carcinoembryonic antigen (ng/ml)</td>
<td>12210</td>
<td>0.0–5.0</td>
</tr>
<tr>
<td>Ca 19.9 (U/ml)</td>
<td>&gt;12000</td>
<td>0.0–37.0</td>
</tr>
</tbody>
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*aPeak value.

Figure 2. Contrast-enhanced CT scan of the liver, showing multiple lesions suggestive for metastasis.

Figure 3. Electrocardiogram was consistent with subacute STEMI.
recent times, it becomes more difficult to separate the risk of deep vein thrombosis brought from this trait, if any, from the one associated with more important thrombophilic states. For arterial thrombosis it appears, from a review of literature cases performed by Girolami and his group, that common risk factors for arterial thrombosis should be disproven before to attribute an arterial event to FXII alone. A 6-year-survey of 58 subjects out of 12 Swiss families with FXII deficiency did not show a difference in thrombosis-free survival between normal and deficient individuals. This report is consistent with a subgroup analysis of the Leiden Thrombophilia Study, who failed to disclose a higher prevalence of FXII deficiency in patients with a first episode of deep vein thrombosis. However, there is some evidence supporting the idea that deficiency of FXII is a stronger risk factor for arterial thrombosis than venous thrombosis. Indeed, Bach et al. have recently shown that reduced activity of FXII is associated with stable coronary artery disease, previous myocardial infarction and acute coronary syndromes, and that this association is independent from other covariates (age, sex, diabetes mellitus, smoking, hypercholesterolaemia and hypertension). Furthermore, Endler et al. have demonstrated, in a large cohort of patients, that FXII activity is strongly and inversely correlated with total and cardiovascular mortality. Even if the authors postulated a U-shaped curve in mortality, this may result from the relative insufficient numerosity of patients in the more severe (i.e. activity of 0–10%) deficiency group (n = 58, <1% of the total sample of 8936 patients), as shown by a very wide hazard risk of 95% confidence interval. However, this apparent paradox seems to have a basic science experimental evidence, since knock-out mice lacking FXII has decreased thrombus formation. Finally, a deficiency of FXII seemed to be prevalent in a series of patients of <45 years of age who suffered from retinal vein thrombosis.

As FXII is known to be a plasminogen activator, reduced fibrinolysis could result from low levels of FXII, and this is thought to be its main putative role in thrombosis.

In summary, the epidemiological data are equivocal, and a role for FXII deficiency in thrombosis cannot still be accepted or refused definitively. In our case, the patient showed traditional risk factors for both arterial and vein thrombosis (advanced age, previous smoke and cancer), so the possibility that the severe FXII deficiency may be merely coincidental cannot be discharged. While awaiting for larger and sufficiently prolonged studies to be performed, we believe that some lessons could be learned from our case.

First, the coincidental presentation of acute myocardial infarction and deep vein thrombosis raises the possibility of the presence of a shared condition that may be the cause of this uncommon clinical picture. Second, if deficiency of FXII is believed to be a risk factor for thrombosis, this very late appearance of the clinical manifestation should suggest that lifelong registry studies should be the best way to disclose the contribution of this condition to clinical events. Third, the presence of a prolonged aPTT in these patients should not discourage, per se, the correct treatment of thromboembolic accidents.

Conflict of interest: None declared.

References


