Acquired Factor XI Deficiency during SARS-CoV-2 Infection: Not Only Thrombosis

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An 80-year-old woman with a positive RT-PCR (reverse transcription polymerase chain reaction) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on nasopharyngeal swab was admitted to our COVID-19 department during the pandemic with fever, dyspnea, and need for oxygen therapy; two large hematomas were present bilaterally in the axillary zones. Her past medical history included Crohn’s disease diagnosed 30 years ago after perforation of the ascending colon, hypertension, bilateral hip replacement, appendectomy, and tonsillectomy; no history of bleeding complications was reported during or after surgical interventions or in the postpartum, and no history of menorrhagia or easy-bruising. One month and a half before admission, she underwent right knee replacement surgery with no complications, no blood units, or plasma transfusions were required. At that time complete blood count and screening clotting test were within normal range.

Investigations on admission were as follows: white blood cell 11,380/mm³ (Neu 10,790; Ly 240); hemoglobin 8 g/dL; mean corpuscular volume 89 fl; platelets 251,000/mm³; PTTr 1.16 (n.v. 0.80–1.21); PTTr 1.49 (n.v. 0.80–1.18); D-dimer 2,161 μg/L (n.v. < 790); fibrinogen 455 mg/dL (n.v. 180–400); C-reactive protein 78.4 mg/L (n.v. < 5.0). A chest computed tomography scan outlined a picture of bilateral interstitial pneumonia with ground-glass areas and thickening of interstitium, consistent with a viral infection; moreover, the presence of hyperdense hematomas in the axillary zones was recorded (thickness 20–30 mm), no active bleeding was detected. Antiretroviral therapy with darunavir and ritonavir was started; hydroxychloroquine was not administered for prolonged QTc on electrocardiogram. Enoxaparin 4000 IU/day was introduced for prophylaxis and continued until hospital discharge.

The isolated prolonged PTTr (silica) was confirmed in day +5 and +7 from admission (1.30 and 1.42, respectively). PTTr (ellagic acid, reagent sensible to factors VIII, IX, XI deficiency) was prolonged too, so a PTTr MIX test was required: the PTTr MIX at time 0 was normal but PTTr MIX at 2 hours at 37°C was above the normal range, consistent with the presence of an inhibitor (►Table 1); the fXI activity was 37% (n.v. 55–150) while fVIII, fIX, and fXII were in the normal range. Detection of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-β2 glycoprotein I) resulted negative. The PTTr MIX test and clotting factors activity was retested 3 days later and the presence of an acquired deficiency of fXI was confirmed. Patient was discharged in good clinical conditions more than 1 month after admission, no thrombotic or bleeding complications occurred during hospitalization.

Inhibitors against clotting factors generally occur in patients with severe congenital deficiencies who underwent periods of replacement therapy. Acquired factor inhibitors in the absence of congenital deficiency are rare events, among them the production of autoantibodies inhibiting fVIII is the most frequent acquired bleeding disorder. On the contrary, inhibitors against fXI have been reported only anecdotally in literature mostly associated to autoimmune disorders, that is, systemic lupus erythematosus, rheumatoid arthritis, Crohn’s disease, membranoproliferative glomerulonephritis, or in association with malignancies, that is, chronic lymphocytic leukemia, gastrointestinal adenocarcinoma, and thymoma; a case of transient acquired fXI deficiency after gynecological surgery has been reported. The risk of bleeding in conditions of fXI deficiency is relatively low and correlation between factor levels and symptoms is very poor; in these persons hemorrhage is usually provoked, exacerbated by trauma or surgical procedures.
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Table 1 Coagulatory and inflammatory parameters

<table>
<thead>
<tr>
<th></th>
<th>Unit</th>
<th>Ref.</th>
<th>March 17</th>
<th>March 21</th>
<th>March 23</th>
<th>March 26</th>
<th>April 7</th>
<th>April 12</th>
<th>April 18</th>
<th>April 21</th>
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<tbody>
<tr>
<td>Thrombin time</td>
<td>Ratio</td>
<td></td>
<td></td>
<td></td>
<td>1.08</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>aPTTr (silica)</td>
<td>Ratio</td>
<td>[0.80–1.18]</td>
<td>1.49</td>
<td>1.30</td>
<td>1.42</td>
<td>1.55</td>
<td>1.40</td>
<td>1.30</td>
<td>1.30</td>
<td>1.24</td>
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<tr>
<td>aPTT MIX time 0</td>
<td>Ratio</td>
<td>[0.80–1.18]</td>
<td></td>
<td></td>
<td>1.17</td>
<td>1.24</td>
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<tr>
<td>aPTT MIX 2 h 37°C</td>
<td>Ratio</td>
<td>[0.80–1.18]</td>
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<td></td>
<td>1.20</td>
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<tr>
<td>aPTTr (ellagic acid)</td>
<td>Ratio</td>
<td>[0.70–1.18]</td>
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<td></td>
<td>1.36</td>
<td></td>
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<td>Factor VIII %</td>
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<td>[50–200]</td>
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<td></td>
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<tr>
<td>Factor IX %</td>
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<td>[65–140]</td>
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<td></td>
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<td>101</td>
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<tr>
<td>Factor XI %</td>
<td></td>
<td>[55–150]</td>
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<td></td>
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<td>37</td>
<td>38.5</td>
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<td>D-dimer µg/L</td>
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<td>[&lt; 790]</td>
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<td></td>
<td>2,161</td>
<td>3,501</td>
<td>2,471</td>
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<td>Fibrinogen mg/dL</td>
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<td>[180–400]</td>
<td>455</td>
<td>541</td>
<td>505</td>
<td></td>
<td>541</td>
<td>568</td>
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<tr>
<td>CRP mg/L</td>
<td></td>
<td>[&lt; 5.0]</td>
<td>78.4</td>
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<td></td>
<td>55.6</td>
<td>12.7</td>
<td>34.7</td>
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</table>

Abbreviations: aPTTr, activated partial thromboplastin time ratio; CRP, C-reactive protein.

In the classical chart of the intrinsic pathway of coagulation, the FXIIa activates the zymogen FXI which in turn activates FIX and so, through a series of enzymatic reactions, it conducts to thrombin formation. It is nowadays well documented that FXII has only a marginal role in the hemostasis in vivo, contributing more to thrombosis, still to demonstrate that pathological coagulation loopwith a mild risk of hemorrhage, as already demonstrated and on the other side disrupting the mechanism driving to the uncontrolled inflammatory overresponse by blunting KKS and complement activation?

By our, at this point, everyday experience and from the still scanty literature in this regard it seems to us that patients with severe pneumonias by SARS-CoV-2 can develop a hypercoagulable condition driving to a higher risk for (micro)vascular thrombosis, still to demonstrate, if true, considering the interface role of FXI in vascular thrombosis and inflammation, the development of therapies inhibiting this factor could be an intriguing leverage on which to act for trying to improve microvascular perfusion, reduce inflammation, and protect organ function during severe infections.

Conflict of Interest
None declared.

References
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