Case Report

Autoimmune protein S activity deficiency following a Q fever

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Anti protein S (anti-PS) antibodies are well-described in patients with systemic lupus erythematosus (SLE) (1–3) but they have also been reported after varicella associated with severe thrombotic complications (4–9), in children with purpura fulminans after an infection other than varicella (5,10), and in patients with human immunodeficiency virus infection (11).

We report here the first case, to our knowledge, of a patient with acute Q fever with a transient deficiency of protein S ascribed to the presence of a circulating autoantibody to protein S.

A 38-year-old man was admitted to hospital (day 0: D0) with dyspnea, right chest pain and fever. He lived in a rural area.

Chest radiography showed diffuse alveolar infiltrates with pleural effusions. The patient developed pneumonia, and was placed on oxygen therapy and antibiotics. Because of the possibility of pulmonary embolism (PE), he was treated with infusion of unfractionated heparin (UFH; 40,000 U/day).

At D0, liver function studies revealed normal levels of ALT and AST, and CRP level was high (219 mg/l; N <3 mg/l). CBC was normal. APTT and PT were normal.

At D1 a chest angioscan indicated the absence of thrombi. At D2, UFH was changed to enoxaparin (40 mg/day). At D5, the levels of ALT, AST and CRP were elevated, APTT and PT were still normal.

At D19, ALT and AST were normal, and CRP was at 13 mg/l. Doppler ultrasonogram of the legs showed no deep venous thrombosis, enoxaparin was discontinued, and the patient had a complete recovery.

Diagnosis of Q fever was confirmed by serological tests: indirect immunofluorescence assay titers were significant for the diagnosis of acute Q fever with high level of specific IgM and IgG (Table 1). These titers were stable at D15, and IgM decreased two months later. Complement fixation test results were irrelevant, because sera were anticomplementary.

Because of the suspicion of PE, a thrombophilia screen was performed. At D2, the coagulation tests revealed a severe deficiency in PS: PS activity <10% (clotting method, Staclot® PS, Diagnostica Stago), free PS antigen 92%, total PS antigen 114% (Asserachrom® total and free PS, Diagnostica Stago). These tests also revealed a moderate deficiency in PC, activity 49% (clotting method, Protein C Reagent®, Dade Behring), antigen 68% (Vidas PC, bioMérieux) whereas PT was normal (INR 1.2). Furthermore, the heterozygous factor V Leiden mutation was present. Otherwise, antithrombin level was normal 88% (Berichrom Antithrombin III Dade Behring), and the prothrombin G20210A mutation was absent. The D-Dimers level (Vidas D-Dimer bioMérieux) was 2,614 ng/ml.

At D10, the anticardiolipin antibodies (ACA) and the antiβ2-glycoprotein I antibodies were measured by home-made ELISA (12). ACA were positive (IgG 232 U, N <36 U; IgM 170 U, N <36 U), whereas the anti-β2-glycoprotein I antibodies were negative. The tests to detect lupus anticoagulant were not performed because of heparin therapy. At D70, ACA had notably decreased (IgG 67 U; IgM 2 U).

The level of PS activity was very low at D2 but it progressively normalized (Table 1), reaching the normal range at D16. The IgM anti-PS antibodies were highly positive at D9 and progressively decreased afterwards. At D19, they were still positive and were undetectable two months later (Table 1). The increase in plasma PS level mirrored the decrease in the IgM antibody titer.

The IgG anti-PS antibodies performed for the same samples were negative.

The D-dimer concentrations were measured at different days: 4,205 ng/ml at D5, 3,963 ng/ml at D11, 2,558 ng/ml at D13, 2,058 ng/ml at D19.

Previous reports demonstrated the occurrence of transient autoantibodies in association with Q fever including antiphospholipid antibodies (13, 14) but the occurrence of anti-PS antibodies had not been reported so far. These transient anti-PS antibodies with a decrease of PS activity have been reported in other infections, especially in varicella (4–9) with severe thrombotic complications.

In agreement with previously reported cases of varicella (4, 9), our data confirm that the acquired PS deficiency is most likely the result of the presence of anti-PS antibodies, because the levels of PS in the plasma mirrored the level of antibodies. The ELISA showed only IgM anti-PS. Furthermore, only PS activity was decreased, the free and total PS antigen remained within normal range. In varicella cases, the authors (5–7, 10) reported...
IgG or/and IgM anti-PS, and in these cases, the free and total PS antigen were also decreased.

At D2, we detected a moderate PC deficiency (activity 49%, antigen 68%). This level stayed stable at D10, D16, and was in the normal range two months later. This finding could be due to an elevated factor VIII level with an apparent PC deficiency or to the transient occurrence of anti-PC antibodies as shown in SLE (15). Remarkably, this patient had numerous thrombophilic factors, i.e. the heterozygous factor V Leiden mutation, a severe PS deficiency, a moderate degree of PC deficiency and ACA, but he had no thrombotic event, and D-dimers were moderately elevated. This could be due to the fact that he received curative doses of UFH (40,000 U/day) for two days (D0, D1) because of suspicion of PE, and then enoxaparin at prophylactic doses (40 mg/day) for 17 days (D2-D19), with neutralization of the thrombogenic risk in this setting.

Thrombophlebitis and PE have occasionally been reported in Q fever (16–20). These unusual manifestations have been associated with antiphospholipid antibodies during the course of acute disease, but none of the reported cases included the analysis of PS levels and the evaluation of anti-PS antibodies. During varicella, most authors have found that the severity of the clinical manifestations correlated with the anti-PS antibodies titers and the severity of PS deficiency, but the antibody titers are not comparable as techniques were different. Moreover, in varicella, the PS deficiency concerns the free and the total PS antigen.

In conclusion, we report here, for the first time to our knowledge, that during Q fever, the appearance of a transient PS deficiency could be due to anti-PS antibodies. Possibly because of heparin therapy, this did not lead to thrombotic events. This case report may be the starting point for further studies to evaluate the occurrence of such a risk in Q fever.

Acknowledgments
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Table 1: Evolution of protein S activity level and anti protein S antibody of the IgM and IgG isotype titers and Coxiella burnetttii antibody titers.

<table>
<thead>
<tr>
<th>Day after admission</th>
<th>Protein S activity (%)</th>
<th>Anti-Protein S antibody</th>
<th>Coxiella burnetti antibody</th>
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<tr>
<td></td>
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<td>IgM (AU)</td>
<td>IgG (AU)</td>
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<tr>
<td>2</td>
<td>&lt;10 ND ND</td>
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<tr>
<td>9</td>
<td>23 120 &lt;5</td>
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</tr>
<tr>
<td>11</td>
<td>40 101 &lt;5</td>
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<tr>
<td>13</td>
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<td>16</td>
<td>68 ND ND</td>
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<tr>
<td>19</td>
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<tr>
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<td>129 9 &lt;5</td>
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References