MULTIPLE RISK FACTORS FOR THROMBOEMBOLISM AND PREGNANCY LOSS IN SYSTEMIC LUPUS ERYTHEMATOSUS: A CASE REPORT

Alexandra Burlui¹, Anca Cardoneanu¹,², Luana Macovei¹,², Elena Rezuş¹,²*

“Grigore T. Popa” University of Medicine and Pharmacy Iaşi
Faculty of Medicine
1. Department of Medical Specialties (II)
Clinical Rehabilitation Hospital Iaşi
2. Ist Rheumatology Clinic
*Corresponding author. E-mail: elena_rezus@yahoo.com

MULTIPLE RISK FACTORS FOR THROMBOEMBOLISM AND PREGNANCY LOSS IN SYSTEMIC LUPUS ERYTHEMATOSUS: A CASE REPORT (Abstract): Systemic Lupus Erythematosus (SLE) is known to pose difficulties when pregnancy is desired. Pregnancy in patients with SLE remains a high risk situation with an increased frequency of fetal loss, preeclampsia, growth restriction and prematurity. We illustrate the case of a young female referred to our clinic by the Institute of Cardiovascular Diseases with a history of miscarriage at 20 weeks of gestation and an episode of pulmonary embolism resulting in multiple peripheral infarctions in the right lung confirmed by spiral CT angiography of the pulmonary arteries. Whereas clinical examination showed no significant changes, routine laboratory assessment confirmed the presence of hemolytic anemia, thrombocytopenia and renal impairment, as well as non-specific inflammatory syndrome. Immunological tests proved positive for the following: antinuclear antibodies, anti-dsDNA antibodies, anti-mitochondrial M2 antibodies, anti-beta2 microglobulin, anti-cardiolipin and lupus anticoagulants. In addition, TPHA and RPR were positive and the C3 fraction of the complement was below normal. Genetic investigations identified the 677 C/T homozygous mutation of the MTHFR gene (Methylenetetrahydrofolate reductase) as well as 675 4G and 844 A/G mutations of the PAI-1 gene (plasminogen activator inhibitor-1). Cases of young female SLE patients positive for the antiphospholipid syndrome remain challenging for clinicians, especially when pregnancy is desired. Keywords: LUPUS, PREGNANCY, MISCARRIAGE, THROMBOEMBOLISM.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease associated with multisystemic involvement and heterogeneous clinical manifestations. During pregnancy, it is best that women with SLE have little or no disease activity. However, pregnancy in SLE patients remains a high-risk situation with an increased frequency of fetal loss, preeclampsia, growth restriction and prematurity. The risk for increased disease activity during pregnancy is greater in women who have active SLE in the months prior to conception (1). Pregnant SLE patients also have a greater risk of developing complications. The presence of the antiphospholipid syndrome (APS) was found to associate with pregnancy loss, prematurity, fetal distress,
growth restriction, preeclampsia or eclampsia, fetal neonatal thrombosis, placental insufficiency as well as myocardial infarction, pulmonary embolism and stroke (2).

Epidemiological studies revealed that antiphospholipid (aPL) antibodies are detected in up to 40% of patients with SLE. In aPL-positive SLE patients, pregnancy morbidity is more common (up to 45%) than in aPL-negative women (2). Lupus nephritis is also thought to increase the risk for adverse pregnancy outcome in APS women (1,2).

**CASE REPORT**

We report the case of a 31-years-old female who was referred to our clinic by the Institute of Cardiovascular Diseases with recent history of pulmonary embolism resulting in multiple peripheral infarctions in the right lung confirmed by spiral CT angiography of the pulmonary arteries. She was diagnosed with APS and treated with both antiplatelet and anticoagulant medication.

Our patient's personal history included active smoker status (7 cigarettes per day for 6 years), miscarriage at 20 weeks of gestation (February 2015) shortly followed by pulmonary embolism. She had no history of substance abuse, alcohol consumption or procoagulant medication.

Clinical examination was normal upon presentation in our service. Routine laboratory tests detected hemolytic anemia, thrombocytopenia (<100,000/mm3) and renal impairment (proteinuria>0,5g/day as well as cellular casts). High levels of inflammatory markers were detected: elevated erythrocyte sedimentation rate (ESR) and C reactive protein (CRP). Immunological investigations identified high antibody titers against β2-glycoprotein I (anti-β2GPI) anticardiolipin (aCL) antibodies, lupus anticoagulants, as well as rheumatoid factor (RF), antinuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA) and anti-mitochondrial M2 antibodies (AMA M2) (tab. I). The above-mentioned parameters were measured through ELISA. In addition, Treponema Pallidum Haemagglutination Assay (TPHA) and Rapid Plasma Reagin (RPR) were positive and the C3 fraction of the complement was below normal.

| TABLE I |

| Autoantibody titers detected in our patient compared to normal values provided by the laboratory. |

<table>
<thead>
<tr>
<th>Parameter (ELISA)</th>
<th>Value obtained</th>
<th>Reference interval/Normal values</th>
<th>Measurement unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-dsDNA antibodies</td>
<td>246.40</td>
<td>0-40</td>
<td>UI/ml</td>
</tr>
<tr>
<td>aPL antibodies (IgG)</td>
<td>63.57</td>
<td>Positive &gt;18</td>
<td>U/ml</td>
</tr>
<tr>
<td>aPL antibodies (IgM)</td>
<td>26.75</td>
<td>Positive &gt;18</td>
<td>U/ml</td>
</tr>
<tr>
<td>Anti-β2GPI antibodies (IgG, IgA, IgM)</td>
<td>37.99</td>
<td>Positive &gt;24</td>
<td>U/ml</td>
</tr>
<tr>
<td>aCL antibodies (IgG)</td>
<td>123.65</td>
<td>0-23</td>
<td>GPL/ml</td>
</tr>
<tr>
<td>aCL antibodies (IgM)</td>
<td>45.54</td>
<td>0-11</td>
<td>MPL/min</td>
</tr>
<tr>
<td>AMA M2</td>
<td>99.74</td>
<td>Positive &gt;24</td>
<td>U/ml</td>
</tr>
<tr>
<td>RF</td>
<td>33.94</td>
<td>Positive &gt;24</td>
<td>U/ml</td>
</tr>
<tr>
<td>ANA</td>
<td>32.05</td>
<td>0-20</td>
<td>UA/ml</td>
</tr>
</tbody>
</table>
Genetic investigations identified the 677 C/T homozygous mutation of the methylenetetrahydrofolate reductase gene (MTFHR) as well as 675 4G and 844 A/G mutations of the plasminogen activator inhibitor-1 gene (PAI-1).

The patient was consequently diagnosed with systemic lupus erythematosus according to the American College of Rheumatology (ACR) diagnosis criteria for SLE revised in 1997, as well as secondary antiphospholipid syndrome. She started oral treatment with hydroxychloroquine 400 mg/day, azathioprine 100 mg/day, clopidogrel 75 mg/day and acenocumarol under careful monitoring of INR values.

DISCUSSION

In our patient, the new-onset SLE consisted of a miscarriage followed by an episode of pulmonary embolism, which are both indicators of secondary APS. Hematological changes included thrombocytopenia and autoimmune hemolytic anemia (AIHA). The pathogenesis of the latter is closely related to the presence of anti-erythrocyte antibodies. Studies showed an association between anti-cardiolipin antibodies and anti-erythrocyte antibodies (3). Complement regulatory proteins CD55 and CD59 protect against erythrocyte lysis. However, they are under expressed in patients with SLE (4).

Our patient had thrombocytopenia possibly due to increased peripheral destruction mediated by antiplatelet antibodies. Alongside this mechanism, two other phenomena have an important role in the appearance of thrombocytopenia: cell sequestration in the spleen and impaired production in the bone marrow (5).

Secondary antiphospholipid syndrome is a common discovery in patients with SLE. APS symptoms may be the first to appear in certain cases. Our patient fulfilled the 2006 classification criteria for APS (Sydney Consensus Statement on Investigational Classification Criteria for Antiphospholipid Syndrome) (6). The PROMISSE Study (Predictors of pRegnancy Outcome: bioMarkers in antiphospholipid antibody Syndrome and Systemic lupus Erythematosus) showed that patients having high titers of lupus anticoagulant antibodies exhibit high risk for adverse pregnancy outcome (7). Another study (8) supported the role of all three antibodies for predicting obstetric complications such as: recurrent miscarriage, early delivery, oligohydramnios, prematurity, intrauterine growth restriction, fetal distress, fetal or neonatal thrombosis, pre-eclampsia/eclampsia, HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet count), arterial or venous thrombosis and placental insufficiency.

SLE is characterized by impaired apoptosis. Patients with SLE may develop autoantibodies such as anti-Ro (SSA) and anti-La (SSB) which can cross the placenta causing neonatal lupus (9). Furthermore, anti-dsDNA antibodies may determine miscarriages by inhibiting the migration and attachment of the trophoblast (10).

Our patient exhibited genetic mutations including the 677 C/T homozygous mutation of the MTFHR gene and the 675 4G and 844 A/G mutations of the PAI-1 gene. The PAI-1 675 4G and 844 A/G mutations are associated with high levels of PAI-1 and impaired fibrinolysis. Recent studies have shown that the 844 A/G polymorphism in the PAI-1 gene identified in our patient may be associated with increased risk for osteonecrosis of the femoral head, acute coronary syndrome and venous thromboembolism (11).
Among other important functions, MTFHR is implicated in DNA methylation and the production of signaling molecules which play a role in embryonic development. Female carriers of the 667 C/T homozygous genotype have low estradiol levels, increased anti-Müllerian hormone concentrations and lower oocyte numbers. Normal MTHFR activity ultimately leads to breaking down the amino acid homocysteine. Increased levels of homocysteine were found to be toxic for embryos (12). The appearance of neural tube defects is associated with both heterozygous and homozygous maternal mutations of the MTHFR gene (13). However, the 677 C/T mutation is not thought to be associated with recurrent pregnancy loss in Caucasian women (14).

The presence of lupus nephritis in our patient is also accompanied by a high risk of fetal loss or complications. Optimal management of lupus nephritis is of major importance to prevent SLE-related adverse pregnancy outcome (15).

CONCLUSIONS
We described the case of a young female diagnosed with SLE after a miscarriage followed by an episode of pulmonary embolism. Clinical examination identified no abnormalities, whereas immunological, hematological and genetic modifications were all present. Our patient expressed her desire for safe successful pregnancy. However, antiphospholipid and anti-dsDNA antibody positivity, as well as our patient's genetic background and the presence of lupus nephritis constitute important risk factors for adverse pregnancy outcome. High SLE activity is a contraindication for pregnancy. Patients in remission for at least 6 months before pregnancy have a better prognosis. The postpartum period as well as the second and third trimesters of pregnancy are associated with high risk for SLE flares. The presence of APS in young female SLE patients pose additional challenges for clinicians, especially when pregnancy is desired.

REFERENCES
1. Tedeschi SK, Massarotti E, Guan H, Fine A, Bermas BL, Costenbader KH. Specific systemic lupus erythematosus disease manifestations in the six months prior to conception are associated with similar disease manifestations during pregnancy. *Lupus* 2015; 24(12): 1283-1292.
Multiple risk factors for thromboembolism and pregnancy loss in systemic lupus erythematosus: a case report


10. Schwartz N, Shoenfeld Y, Barzilai O et al.. Reduced placental growth and hCG secretion in vitro induced by antiphospholipid antibodies but not by anti-Ro or anti-La: studies on sera from women with SLE/PAPS. Lupus, 2007; 16(2): 110-120.


LIVER SUBCAPSULAR HEMATOMA: A RARE CAUSE OF SUDDEN UNEXPECTED DEATH

The spontaneous subcapsular hematoma of the liver is very rare. There are only a few reported cases in the literature. Most reported cases of liver hematoma often occur during pregnancy as part of the hemolysis, elevated liver enzymes, and low platelet count syndrome. The other causes may be due to amylosis, rupture of hepatocellular carcinoma, adenoma, focal nodular hyperplasia, hemorrhagic cyst, or hemopathy. Idiopathic spontaneous subcapsular hematoma is a rare and often fatal condition. A 43-year-old woman having Steinert disease died because of a fatal spontaneous liver hemorrhage occurring without any traumatism. Was not find any apparent cause that could explain this hemorrhage even after a histological study of the liver (Oualha Dorra, Aissaoui A., Belhaj Meriam, Mesrati, Mohamed A, Moussa Adnene, Salem N, Zakhama A, Chadly A. Am J Forensic Med & Pathol. 2017; 38 (1): 9–10).

Diana Bulgaru Iliescu, A. Knieling

NEWS