BIiochemical Markers in Pregnancy Associated with Sjogren's Syndrome and Thrombophilia

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Sjögren's syndrome (SS) is a multisystemic disease mainly characterized by the hypofunction of the lachrymal and salivary glands and can be either primary or secondary, when related to other autoimmune pathologies. We present the case of a 35-year-old female admitted in the Department of Obstetrics and Gynecology for pregnancy monitoring. The patient had a personal history of a spontaneous abortion one year prior to admission at 5 months of gestation and a maternal history of SS. A multidisciplinary approach with solid obstetrical, rheumatological and neonatal monitoring is essential for best outcomes of the mother and fetus. An early detection of maternal and fetal immune-mediated threats and judicious use of medication is essential in women with autoimmune diseases who plan conceiving.

Keywords: Sjögren's syndrome, thrombophilia, pregnancy, multidisciplinary approach

Sjogren's syndrome (SS) is a multisystemic disease mainly characterized by the hypofunction of the lachrymal and salivary glands and can be either primary or secondary, when related to other autoimmune pathologies [1]. The clinical manifestations are both glandular consisting of xerostomia, xerophthalmia, swelling of the parotid and submandibulary glands and extra-glandular such as arthritis or arthralgias, vasculitis, Raynaud phenomenon, respiratory, gastrointestinal, neurological, hematological and renal involvement [2,3].

Mainly a women's disease, with a female: male ratio of 9:1 and a prevalence in the general female population of 0.1 – 4.8%, SS is the perfect example of sex hormones' involvement in the disease pathogenesis. Estrogens-deficient individuals provide inefficient protection of glandular acinar cells against apoptosis and effective clearance, leading to failure of self-tolerance and autoimmunity engagement. Several recent studies report the probability of pregnancy associated complications in women with SS as well as on disease outcome. While SS does not influence fertility, the presence of anti-Ro (anti-SS-A) and/or anti-La (anti-SS-B) antibodies as immunological hallmark of the disease, the disease activity and subsequent treatment may significantly impact fetal and maternal outcome [4, 5].

Anti-Ro and anti-La antibodies are of particular importance due to the association with congenital heart block (CHB), neonatal lupus (NL), spontaneous abortions, intrauterine growth restriction (IUGR) and increased frequency of cesarean delivery. These antibodies are considered to be a model of the transplacentar acquired autoimmune phenomenon as they start crossing the placenta around 16 weeks of gestation and are responsible of the immune –mediated attack of the cardiac conduction system and able to induce myocarditis, arrhythmias, endocardial fibroelastosis or cardiomyopathy in the fetus. The presence of anti-Ro/SS-A antibodies in the first pregnancy determines a 1-2% risk of CHB and substantially higher of 10-20% with subsequent pregnancies if the first child is affected, and more strongly associated with the presence of anti-52kDa Ro/SS-A and anti -La/SS-B antibodies rather than with anti-60kDa Ro/SS-A antibodies [6].

Experimental part

Case report

We present the case of a 35-year-old female admitted in the Department of Obstetrics and Gynecology for a regular medical examination. The patient had a personal history of a spontaneous abortion one year prior to admission at 5 months of gestation and a maternal history of SS.

The local exam revealed vulva and vagina with pregnancy-specific hormone impregnation, cervix with external orifice in the transverse slit with no macroscopic lesions. The vaginal exam combined with abdominal palpation showed a cervix with closed external orifice, enlarged globular uterus, specific for a 9-week pregnancy, unpainful. The ultrasonographic examination revealed an intrauterine gestational sac with a live, unique 9-week fetus.

Following the anamnesis and the clinical examination the diagnosis of secundiparous, pregnancy of 9 gestational weeks in evolution, with living, unique fetus is established; spontaneous abortion with fetal mortality at 5 months in the past. As an attentive anamnesis identified the presence of oral dryness and the maternal history of connective tissue disease, in this regard, besides the paraclinical pregnancy-specific investigations, autoimmune tests and a rheumatologic evaluation were imposed.

Routine hematological investigations showed blood group AB (IV), Rh positive, complete blood count and coagulogram in normal parameters. Biochemical assays have revealed minor changes in serum sodium of 135.6 mmol / L and the albumin / globulin ratio 1.34 (normal

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Variable	During pregnancy	6 months after birth	Reference range
ANA	1/240	1/320	1/80
Anti-ds DNA antibodies	negative	negative	Negative
Anti-Sm antibodies	negative	negative	Negative
Anti-Ro/SS-A antibodies	99 U/mL	264 U/mL	>10 U/mL
Anti-La/SS-B antibodies	1.6 U/mL	4 U/mL	>10 U/mL
Complement C3	84 mg/mL	43 mg/mL	90-180 mg/mL
Complement C4	10 mg/mL	3 mg/mL	10-40 mg/mL
RF	116 U/mL	184 U/mL	0-14 U/mL
Anti – CCP antibodies	negative	negative	Negative
CRP	0.2 mg/dL	0.8 mg/dL	< 0.5 mg/dL
Crioglobulins	Absent	Present +++	Absent

Table 1
SPECIFIC AUTOIMMUNE LABORATORY EVALUATION

range 1.39-2.23). The TORCH profile for toxoplasma, rubella, cytomegalovirus and herpes virus was negative, as well as HIV and hepatitis B and C testing. Double and triple test for prenatal screening showed a decreased risk for trisomy 21, trisomy 18 and neural tube defects.

Taking into account the history of pregnancy loss we ruled out the possibility of an associated antiphospholipid syndrome: lupus anticoagulant, anticardiolipin antibodies and anti-β2GPI were negative.

Thrombophilic profile has been highlighted by factor V Leiden mutation-positive heterozygous mutation of prothrombin (factor II) -positive, heterozygous MTHFR gene, the mutation-C677T heterozygous genotype, A1298C mutation-negative, PAI-1 gene heterozygous genotype. Normal values for antithrombin III 128% (normally over 80%), protein C 107% (normally 70-130%), protein S 77% (normally 55-140%) were registered.

The clinical rheumatological examination revealed xerostomia and xerophthalmia with a positive Schirmer test and mild arthralgias of the small joints of the hands.

Specific autoimmune laboratory evaluation of the patient is figured in table 1 (table 1).

Ultrasound of the parotid glands was performed and revealed an aspect of bilateral inhomogeneity of the salivary parenchyma, through the presence of multiple hypoechoic areas larger than 2mm, of round-ovalar shape, by diminishing the presence of arthralgias. Baby-aspirin 75mg/day was administered for thrombophilia associated risk. At 26 weeks, treatment of interphalangeal arthralgia of the hands associated with marked inflammatory syndrome is intended by the administration of anti-inflammatory medication, but without a positive result. In this case, treatment with dexamethasone is restored as well as with hydroxychloroquine with a definite beneficial effect. Clinical and paraclinical monitoring has been systematically performed, taking into account maternal-fetal prognosis under such circumstances. Fetal antepartum monitoring has as targets fetal biometry, heart rate, fetal movement and respiration, placental appearance and amniotic fluid production. On the other hand, rheumatological evaluation followed the haemo-leucogram, titer of anti-Ro, La antibodies and RF, complement C3 and C4 values, glandular and extra-glandular involvement.

The case was completed in terms of background pathology and gestation completion at 35 gestational weeks, through cesarean surgery, with a live fetus, of female sex, 2330 g, Apgar score of 9. The postoperative outcome for both the fetus and the mother was very good. At the patient's request, we practiced bilateral fallopian tubal ligature with concomitant cesarean surgery.

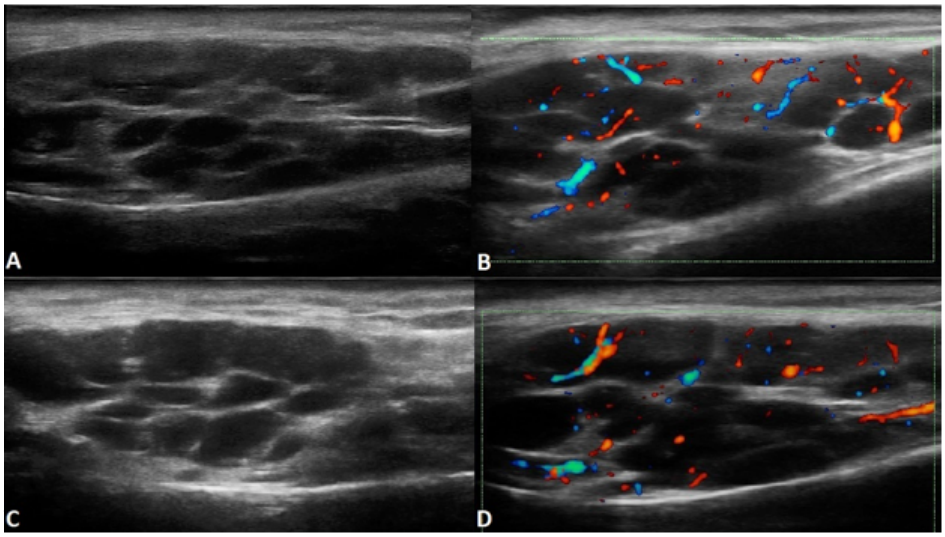

Fig. 1 (A, B, C, D): Right parotid gland - grey scale (A) and power Doppler (B) with marked inhomogeneous pattern and hypervascualarity . Left parotid gland -grey scale (C) and power Doppler (D) -the same cystic aspect with grade 2 power Doppler signal

Currently, the baby is clinically healthy, with cardiologic specific investigations without pathological changes.

At 2 weeks postpartum the patient developed right parietal ictus with remitted left hemiparesis and convulsions. The patient was admitted to the Department of Neurology. The angiography revealed signs of flux turbulences through the right parietal cortical veins and minimal bleeding at the level of the right parietal girus. The patient was started on methylprednisolone 16 mg per day, hydroxychloroquine 400 mg per day and enoxaparin 40 mg per day.

Six months later the patient developed purpura located at the lower limbs and other smaller eruptions on the arms and abdomen. The laboratory tests showed cryoglobulinemia, high ESR, low C3 and C4 complement, high titers of anti- Ro and La antibodies, negative lupus anticoagulant and anticardiolipin antibodies, as figured in table 1. The patient was started on high dose glucocorticoids, azathioprine 100 mg per day, hydroxychloroquine 400mg per day and plasmapheresis with disappearance of purpuric lesions and favorable response of Sjögren syndrome (fig. 2).

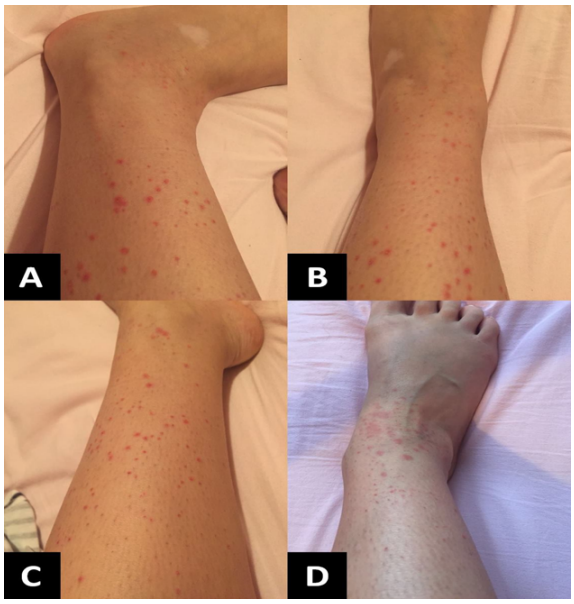

Fig. 2 (A, B, C, D): A, B, C – Purpuric lesions located on the left calf, D -Purpuric lesions located on the right foot

Results and discussions

Pregnancy is associated with the suppression of the humoral and cellular immunological function in order to allow the implantation of the paternal semiallogenic fetal graft, non-self to the maternal organism. The pregnancy is both a pro-inflammatory and an anti-inflammatory state, depending on the trimester. The beginning of the pregnancy is considered pro-inflammatory due to implantation and placentation processes. The second trimester, characterized by rapid growth and development of the fetus is anti-inflammatory. The birth is defined by an influx of immune cell in the myometrium in order to trigger an anti-inflammatory process [7].

An anti-inflammatory component of the pregnancy is the suppression of helper 1 and cytotoxic T cells which decreases the production of interleukin 2, interferon â and tumor necrosis factor. Pregnancy induces the predominance of T helper 2 cells to the detriment of T helper 1 cells, explaining the remission of certain autoimmune diseases during pregnancy such as rheumatoid arthritis, multiple sclerosis and Hashimoto thyroiditis [8]. The stimulation of T helper 2 cells leads to the increased secretion of interleukins 4, 6 and 13. Pregnancy hormones alter the immune cell response, estrogens increase the response of T cells, androgens decrease it, while progesterone has an immunosuppressive effect [9].

Some immune-mediated diseases may be activated as a result of anterior pregnancies. The fetal cells and DNA are detectable in the maternal blood since the beginning of the pregnancy. Fetal cells can persist in the maternal blood and organs even after birth and can stimulate the autoantibodies or can become grafted into maternal tissues, thus emphasizing on the fact that fetal cells may be related to the predilection for autoimmune diseases. Grafted fetal stem cells have been found in maternal tissues of women with autoimmune thyroiditis, systemic sclerosis, systemic lupus erythematosus and rheumatoid arthritis.

Autoimmune conditions, mostly systemic lupus erythematosus and SS are likely to severely impact the evolution of a pregnancy [10]. Hereby, we took into consideration a case with maternal background of SS, asymptomatic before pregnancy. While most studies report primary SS onset before or after pregnancy, in our case the diagnosis was established upon the appearance of symptoms during pregnancy. The real onset was most probably before, but as cited, SS is a disease with a diagnosis frequently delayed for years, due to some common symptoms which may also be encountered in the general population (dryness, asthenia, diffuse/localized pain).

SS in pregnancy can either complicate the gestation or aggravate the autoimmune disease in the intra or mostly postpartum period. In our case, among pregnancy outcome complications we mention early delivery at 35 weeks of gestation, through cesarean section as well as a lower birth weight. Although the risk of CHB was considered increased in our patient due to the high titer of anti-SS-A/Ro antibodies in the mother, as well as low complement C3, probably the administration of dexamethasone decreased significantly the transplacentar passage and lowered the titer so their pathogenic influence was not recorded upon the conduction system. The presence of anti-Ro and La antibodies in the maternal serum is responsible for the development of postpartum complications such as neonatal lupus and CHB but administration of fluorinated glucocorticoids that are not inactivated by the placentar hydroxylase significantly reduce the immune-mediated effect on the nodal tissue, even though the treatment is not routinely recommended due to frequent side effects. In this case, we did not record any maternal or fetal adverse effects related to dexamethasone administration [11].

Maternal antibodies can be transported through the placenta as early as 11 weeks of gestation leading to the development of cardiac abnormalities, rash, liver and hematological abnormalities. Only the cardiac manifestations persist after 6-8 weeks post-natal while the rest of the features disappear due to the clearance of antibodies [12].

Several hypotheses of the molecular mechanism leading to CHB have been proposed, one of the theories accepted being that anti-Ro52 antibody produces disturbances in signal conduction due to the direct impact on the calcium homeostasis in the fetal heart [13].

Administration of hydroxychloroquine was effective in terms of joint involvement, sicca syndrome and constitutional symptoms. More recently, it is reported to

decrease inflammatory and immune biomarkers such as ESR, CRP, RF and anti-Ro and La antibodies and considered safe during pregnancy [14].

As central nervous system involvement is a matter of considerable debate, but with several cases of stroke, transverse myelitis or multiple sclerosis-like disease described in literature in SS, we interpret the neurological event that occurred 2 weeks postpartum as associated to the existing thrombophilia, only after the exclusion of antiphospholipid syndrome [15].

Postpartum outcome of the patient 6 months after delivery with increased autoimmune activation, addition of cryoglobulinemic vasculitis in the presence of high titers of RF and low complement was consistent with several case reports found in literature that note Sjögren syndrome aggravation following pregnancy [16].

Conclusions

Anti-Ro (SS-A) and anti-La (SS-B) antibodies play an important role in the diagnosis and monitoring of autoimmune diseases associated with pregnancy. Dexamethasone treatment was beneficial for both the fetus in preventing CHB and its maturation, as well as for the mother in alleviating glandular and extra-glandular symptoms of Sjögren's disease.

With all the diagnostic and treatment impairments that this case has raised during gestation and despite the worsening of the autoimmune disease following delivery, the general condition of the patient and the intrauterine condition of the fetus was controlled. The fetus was extracted through cesarean section, with grade I prematurity and did not require neonatal resuscitation, being adaptable to the very good external environment.

A multidisciplinary approach with tight obstetrical, rheumatological, and neonatal monitoring is essential for best outcomes of the mother and fetus. An early detection of maternal and fetal immune-mediated threats and judicious use of medication is essential in women with autoimmune diseases who plan conceiving.

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