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Autoimmune lymphoproliferative syndrome in pregnancy: A case of favorable mother–fetal outcome in a well-controlled disease

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Abstract

The autoimmune lymphoproliferative syndrome (ALPS) is a disorder of abnormal lymphocyte survival caused by the dysregulation of the Fas apoptotic pathway. The Fas gene is expressed at the maternal–fetal interface and is involved in the regulation of immune response and implantation. Altered Fas expression may result in altered apoptosis and, ultimately, affect both the immune response and implantation; it is in fact associated with recurrent pregnancy loss, preterm premature rupture of the membrane and pre-eclampsia. Currently, there are over 500 cases of ALPS reported worldwide from various racial and ethnic backgrounds. Up to date, the published work contains no specific reports on pregnancy outcome in women affected by ALPS. We present a case of full-term uneventful pregnancy in a patient affected by ALPS. A specific clinical follow-up in a pregnant woman with primary immunologic disease is suggested.

Key words: autoimmune lymphoproliferative syndrome, Fas, pregnancy, primary immunologic disease.

Introduction

Autoimmune LYMPHOPROLIFERATIVE SYNDROME (ALPS) is, generally, an early onset (24 months of age) primary immunologic disease, consisting of a disorder of abnormal lymphocyte survival caused by the dysregulation of the Fas–apoptotic pathway.[1] Five hundred cases of ALPS are currently reported worldwide from various racial and ethnic backgrounds.[2] The syndrome is characterized by autoimmunity, non-malignant lymphoproliferation, secondary malignancies (an increased risk of B-cell lymphoma), as well as by the presence of a rare T-cell population expressing T-cell receptor (TCR)-$\alpha\beta^+$ $CD3^+$ $CD4^-$ $CD8^-$, known as double-negative (DN) cells, in the peripheral blood.[2,3] Lymphoproliferation may present as lymphadenopathy, splenomegaly and hepatomegaly. Over 70% of patients develop an autoimmune disease, commonly multilineage cytopenias (e.g. hemolytic anemia, thrombocytopenia, autoimmune neutropenia).[4] Other autoimmune manifestations such as nephritis, hepatitis, urticaria, arthritis, colitis and pulmonary fibrosis are less frequent. Fas and Fas ligand (FasL) interact through the Fas-activating death domain (FADD), triggering the caspase cascade, culminating in DNA degradation, proteolysis and apoptosis.[5] During pregnancy, the uterus and the placenta are immunologically privileged sites in which the immune activity is effectively diminished; immune cells apoptosis has been identified as a mechanism for maintaining immune privilege.[6] Fas and the FasL system is expressed at the maternal–fetal interface and it is involved in pregnancy physiology in the first trimester.[7] On the other hand, its dysregulation is related to pathological processes such as recurrent pregnancy loss, premature rupture of the membrane and pre-eclampsia.[8–10] Moreover, the presence of an autoimmune disease is also associated with clinical conditions that negatively affect pregnancy (e.g. thrombocytopenia, infections and, in particular, complications due to

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surgical cuts). We report a case of full-term uneventful pregnancy in a patient affected by ALPS and suggest a specific follow-up in a pregnant woman with primary immunologic disease.

Case Report

A 23-year-old Caucasian woman, with a body mass index (BMI) of more than 30, zero para and known to have ALPS, was referred to the high-risk obstetric unit of our department at 13 weeks of gestation. Her medical history began at 22 months of age, when she presented splenomegaly, neutropenia, thrombocytopenia and autoimmune hemolytic anemia. She was transfused and treated with corticosteroid therapy. Nine years later, due to an episode of severe hemolysis resistant to medical treatment, she underwent splenectomy and was treated with 1 000 000 IU of benzylpenicillin every 15 days in order to avoid post-splenectomy sepsis. Until the age of 23 years, she was administrated cycles of prednisone at different doses and 200 mg of cyclosporin daily. During this period, she presented different exacerbation of the disease with thrombocytopenia (platelets, <5000), arthritis and eczema. In 2012, she stopped the treatment with cyclosporin because of high blood pressure and remained free from symptoms.

The patient presented at our department at 13 weeks of pregnancy on current treatment with 12.5 mg of prednisone daily, 1 000 000 IU of benzylpenicillin every 15 days and 5 mg of folate daily; because of the lack of teratogenicity of prednisone and benzylpenicillin and their positive effect on the maternal disease, assumption of the regular drugs was recommended till delivery. Pregnancy, although unplanned, started spontaneously during a remission phase after a 12-month disease. All laboratory blood tests were within normal range. Immunologic markers, lupus anticoagulant, antiphospholipid and anti-Ro antibodies were negative; antinuclear antibodies were positive. She underwent an abdominal ultrasound scan including lymph node evaluation and a cardiovascular examination that were unremarkable. During pregnancy, the following control schedule was proposed in an outpatient regimen: every 2 weeks maternal clinical parameters (blood pressure, heart frequency, weight increase) and blood tests (red blood cells, white blood cells and platelets count; assessment of acute-phase reactants and evaluation of liver and kidney function) were measured to monitor the mother's autoimmune hemolytic anemia and thrombocytopenia; every 3 weeks a fetal ultrasound scan was performed (in order to assess fetal growth, spleen size and middle cerebral artery flow) until the third trimester in order to exclude an *in utero* onset of fetal disease. At 16 weeks of gestation, ultrasound scan did not show fetal abnormalities, except for a hyperechoic bowel. The patient underwent planned genetic counseling, during which she was informed about the autosomal dominant transmission of ALPS. Cystic fibrosis screening of both parents was performed and tested negative. Amniocentesis was carried out without any complications and the fetal karyotype was normal (46, XY). At 22 weeks of gestation, the morphologic ultrasound evaluation did not show fetal anomalies and fetal spleen size appeared normal. The ultrasounds performed until the third trimester did not show signs of hepatosplenomegaly and fetal anemia. From the 30th week of gestation, fetal cardiotocography was performed once a week. At 36 weeks, the patient was hospitalized for a threatening preterm delivery. During admission, routine analysis and fetal scans were in the normal range. An emergency cesarean section was performed at 38 weeks due to the diagnosis of a genital wart and a not reassuring non-stress test. She delivered a healthy boy weighing 3706 g; his blood count was completely normal. After delivery, the clinical condition of the patient and the blood laboratory tests were within normal range. The patient received antibiotic therapy (cefazolin 2 g, metronidazole 500 mg, t.i.d. for 5 days) and thromboprophylaxis with enoxaparine 6000 once a day for 6 weeks. After 6 days, the abdominal wound showed signs of local infection and dehiscence. A pelvic and abdominal ultrasound was performed to exclude a pelvic abscess and the presence of free intraperitoneal fluid; the uterus was regularly positioned. After 4 weeks, a surgical curettage of the wound and a re-suture were performed. A few days later, the patient was in good clinical condition and discharged back home. The follow-up at 6 months from delivery was negative for the mother and the baby.

Discussion

Autoimmune lymphoproliferative syndrome was first identified as a clinical entity by Canale and Smith in 1967.[11] In 1992, a genetic mutation in the 'death receptor' Fas was discovered in a mouse model exhibiting lymphoproliferation. Shortly after, mutations in the same molecule were shown to underlie the human disease, and was known as ALPS thereafter. The main molecular causes of ALPS are mutations in the death

receptor Fas (80%), its ligand (2%) and caspase-10 (2%).[1] In childhood, the mutations result in the accumulation of proliferating lymphocytes triggering chronic lymphadenopathy, splenomegaly, multilineage cytopenias secondary to sequestration and autoimmune destruction, and to an increased risk of B-cell lymphoma. The latest National Institutes of Health (NIH) revision of ALPS diagnostic criteria from the 2009 international workshop is divided into two required and six accessory criteria. Required criteria include the presence of lymphadenopathy and/or splenomegaly, and elevated TCR-$\alpha\beta^+$ DNT cells. Accessory criteria are subdivided into primary ones, which include an abnormal lymphocyte apoptosis assay and the presence of pathogenic mutations in the Fas pathway genes; and secondary criteria, which include the presence of elevated circulating biomarkers, characteristic histopathology, the combined presence of autoimmune cytopenias, polyclonal hypergammaglobulinemia and family history compatible with ALPS.[2] Over 70% of patients with ALPS have identifiable mutations in Fas pathway genes.[4] In order to downregulate the normal immune response, activated B and T lymphocytes increase Fas expression and activated T lymphocytes increase the expression of FasL. Both Fas and FasL are localized in the chorionic villi and the decidual layers. The Fas gene is known to be expressed at the maternal–fetal interface and to play an important role in the immune response regulation. The T-helper (Th)1/Th2 activity ratio is critical for normal pregnancy. The apoptosis of cytotoxic T lymphocytes is essential for the maternal immune tolerance during pregnancy. It has been reported that the activation of T lymphocytes by foreign antigens induces the expression of Fas, which upon binding to FasL, initiates a cascade of the apoptotic pathway that eliminates lymphocytes and suppresses the immune response.[12] The role of these mechanisms has been recently discovered in physiological pregnancy development and maintenance. Cell death through apoptosis is essential for maintaining the normal invasion of the embryo, and for the embryo immune tolerance.[7] Implantation involves proliferation, differentiation and apoptosis in order to accommodate the growing conceptus. Rapid morphologic changes that influence the placenta development take place in the maternal deciduas.[13] The decidua undergoes a characteristic temporal and spatial pattern of regression through the process of apoptosis, which is also essential for successful fetal–placental development.[7] Some studies on mice deficient in Fas–FasL show that this defect has no adverse effect on pregnancy outcome.[14] Conversely, disturbances in programmed cell death in the placenta seem to be associated with abnormal pregnancy outcome: the loss of Fas expression and defective apoptosis are associated with recurrent pregnancy loss, preterm premature rupture of the membrane and pre-eclampsia.[8–10] Furthermore, lymphoproliferation with anomalies of the Fas–FasL system characterized by autoimmunity that resembles systemic LES (i.e. thrombocytopenia, autoimmune hemolytic anemia, nephritis), together with an increase in the risk of infections, may negatively affect pregnancy. Up to date, the published work contains no specific reports of pregnancy outcome in women affected by ALPS. Only a case of *in utero* early onset of fetal ALPS in a family with a novel Fas mutation has been reported.[15] We will describe a pregnant patient diagnosed with ALPS at 24 months according to the NIH criteria: splenomegaly, neutropenia, thrombocytopenia and autoimmune hemolytic anemia. Pregnancy had a physiological course, despite the genetic defect of the maternal FADD system; the only complication was the infection of the surgical wound probably due to multiple risk factors linked to ALPS, corticosteroid therapy and a high BMI. ALPS complications were not detected during pregnancy, or in the first 6 months of follow-up after delivery. In our opinion, the uneventful pregnancy may be related, above all, to the long remission phase of the disease at the onset of pregnancy and to the appropriate medical treatment during pregnancy; we suggest monitoring both the mother for autoimmune hemolytic anemia and thrombocytopenia during pregnancy with an appropriate surveillance plan and the fetus (fetal spleen size and middle cerebral artery flow), in order to exclude an early onset of *in utero* disease. The timing and modality of delivery are an individual choice which derives from a balance between primarily obstetric indications, the maternal risk of infections and the possible consequences on the fetus. Further knowledge on pregnancy in women affected by ALPS may improve the insight into mechanisms involved in fetal–placental pathologies.

Disclosure

All authors have declared no conflicts of interest.

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