CASE REPORTS

Fetal cardiofibroelastosis - a consequence of anti-Ro maternal transfer during pregnancy. Case report and review of the literature

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ABSTRACT

With scarcely any reports published on the association of fetal endocardial fibroelastosis and Ro antibodies maternal transfer during pregnancy, this subject continues to raise concern among health care providers around the world, especially when neonatal lupus syndrome is taken into consideration as the main diagnosis. Fetuses with congenital atrioventricular block have a risk of intrauterine fetal demise and the concern comes from a variety of factors that show significant association between the presence of maternal antibodies to SS-A/Ro during pregnancy and their children serum level of these antibodies. Nevertheless, fetal endocardial fibroelastosis plays an important role in altering ventricular diastolic function and ventricular development in children and neonates.

Methods. Medical literature was searched on PubMed and Medline using key words such as fetal endocardial fibroelastosis, anti-Ro antibodies in pregnancy and neonatal lupus syndrome and over 200 articles were taken into consideration, with 17 of them included in the final review. The clinical case included in this paper was referred to the Department of Maternal Fetal Medicine, Filantropia Clinical Hospital in Bucharest, during the second pregnancy after a first pregnancy that resulted in stillbirth with congenital heart block and fibroelastosis as a result of the maternal diagnosis of Sjogren's syndrome with transplacental transfer of SS-A/Ro antibodies.

Keywords: fetal endocardial fibroelastosis, anti-Ro antibodies, pregnancy, neonatal lupus syndrome

INTRODUCTION

It was suggested that antibodies to SS-A/Ro occupy a crucial role in the diagnosis of neonatal lupus syndrome, as congenital heart block (CHB) frequently coexisting with cutaneous lupus are the main clinical components illustrating this syndrome [1]. According to Reed et al., anti Ro/La antibodies that are discovered in the serum of the mother could also be found in their neonates serum, a notion promoted by the study of 12 children diagnosed with congenital heart block, 16,67% of them associating cutaneous lupus lesions [1]. The same results were stated earlier, in 1983, during a study conducted by Scott et al., in which it was described that antibodies to SS-A/Ro are vertically transmitted and they are likely to be associated with congenital complete heart block [2].

CASE REPORT

A 30-year-old female G2P2, with a first pregnancy that ended up in stillbirth at 23 weeks of gestation as a result of transplacental passage of maternal anti-Ro antibodies that caused congenital heart block with fetal hydrops and heart failure, presented in our clinic for antenatal care during her second pregnancy. The patient was diagnosed with Sjogren's syndrome that associated anti-Ro antibodies during her first pregnancy. After the second pregnancy confirmation at 6 weeks gestation, prophylactic Hydroxychloroquine was proposed.

Examination

First trimester ultrasound assessment was within normal range. The patient was constantly moni-

tored and at 22 weeks of gestation, the ultrasound assessment identified no fetal structural anomalies, except recurrent intermittent second- and third-degree atrioventricular block with intermittent fetal bradycardia with no signs of cardiac insufficiency or fibroelastosis.

Management

Dexamethasone therapy was proposed at a daily dose of 4 mg, given to the patient orally, daily, and the treatment was continued throughout the rest of pregnancy. The patient gave birth via cesarean section after premature rupture of membranes at 36 weeks of pregnancy. Birth weight was 2.6kg and Apgar score at 5 minutes was 9. Neonatal anti-Ro antibodies were positive, the neonatal electrocardiogram showed a third-degree atrioventricular block with ventricular rate of 80 beats per minute and neonatal echocardiography showed no cardiac anomalies, except mild pericardial effusion. Neonatal treatment included steroids, immunoglobulin, isoprenaline and diuretic and nearly half a year later, no ventricular dysfunction was present.

DISCUSSION
Definition of endocardial fibroelastosis

According to Zhang et al, endocardial fibroelastosis (EFE) is defined as extreme expansion of fibrous and elastic tissue that leads to endocardium widening, a process that mainly affects infants and children, altering ventricular diastolic function and ventricular development [3]. The etiology has been described as multifactorial, such as genetic X-linked recessive, infectious, viral, but also autoimmune with the association of anti-Ro and anti-La antibodies, although a large number of the cases remains idiopathic [4]. As endocardial fibroelastosis is still considered uncommon, the incidence and prevalence are not well described in the current literature. Lipshultz et al. published a scientific statement from the American Heart Association in 2019 in which the incidence of pediatric cardiomyopathy is established as 1 per 100 000 children, thus including endocardial fibroelastosis [5]. The main pathophysiologic factor is accumulation of acellular fibrocartilaginous components in the endocardium, especially in the subendothelial lamina, to such a degree that macroscopically, the normal transparent endocardium becomes bright white, frequently associated with myocardial increased thickness and valvular impairment [4,5]. The endocardium consists of five layers and during the process of cardio-fibroelastosis all the layers are impaired, with addition of elastin and collagen fibers, a process that was studied by Fishbein et al. by staining elastic fibers with silver tetraphenyl-porphin sulfonate [6]. Although

the clinical presentation of cardio-fibroelastosis is complex, especially during intrauterine life, Seki et al. investigated 52 pediatric heart transplant cases and recommended pathological criteria for the diagnosis of cardio-fibroelastosis as they are seen in Table 1 [7].

TABLE 1. Criteria of pathological diagnosis of cardio-fibroelastosis proposed by Seki et al. [7]

- Lack of auxiliary inherited malformations
- Lack of concealed vascular, metabolic, or inflammatory diseases
- Spherical or dilated left ventricle (LV)
- Disseminated expansion of left ventricle endocardium
- Left ventricle papillary muscles reallocated ascensive and close to the left atrium
- Widened free edges of mitral valve leaflets
- Cluster of elastic fibers in the endocardium

The role of SS-A/Ro antibodies

When systemic autoimmune diseases are diagnosed, among the most prevalent antibodies that are found in these syndromes, are the antibodies against ENA (extractable nuclear antigens), the most acknowledged of them being Anti-Ro/SSA and anti-La/SSB antibodies. Besides being one of the most important criteria of diagnosis of Sjögren's syndrome, according to Wenzel et al., the anti-Ro/SSA and anti-La/SSB antibodies are also found in a high percentage in the serum of these patients [8]. First described in 1961 by Anderson et al., anti-Ro/SSA and anti-La/SSB antibodies precipitate when they are adjacent to antigens which are found in the salivary and lacrimal glands of patients with Sjogren's syndrome [9]. In a paper published by Schulte-Pelkum et al. in 2009, it was stated that although anti-Ro/SSA antibodies are associated with numerous systemic autoimmune diseases (Table 2), Ro60 (SS-A) and Ro52 embody two different autoantibody structures [10].

TABLE 2. Systemic autoimmune diseases that associate anti-Ro/SSA antibodies proposed by Schulte-Pelkum and al in 2009 [10].

- Dermatomyositis
- Mixed connective tissue disease
- Polymyositis
- Rheumatoid arthritis
- Sjögren's syndrome
- Systemic sclerosis
- Systemic lupus erythematosus

SS-A/Ro antibodies and congenital heart block

Ho et al. studied eight patients with congenital heart block, 87,5% of them associating SS-A/Ro ma-

ternal antibodies [11]. The pathogenesis of congenital heart block associated with SS-A/Ro maternal antibodies consists of abnormal signal transmission of the atrio-ventricular node as result of the inflammatory process induced by vertical transmission of SS-A/Ro maternal antibodies [11]. Nevertheless, in the PR Interval and Dexamethasone Evaluation (PRIDE) prospective study that was published in 2008, 127 patients with anti-SSA/Ro antibodies were evaluated emphasizing the association between congenital heart block in offspring's and maternal antibodies to SSA/Ro-SSB/La [12]. As congenital heart block was better identified between 18 and 24 weeks of gestation, intrauterine treatment could be established, with options such as prednisone, dexamethasone, and/or plasmapheresis and weekly heart ultrasound follow-up in order to assess early manifestations of cardiac deterioration such as mitral or tricuspid regurgitation, left ventricular dilatation, inadequate contraction, pericardial effusion or hydrops fetalis [12]. According to Bordachar, pregnant women with anti-Ro/Sjögren's syndrome antigen A (SSA) and anti-La/Sjögren's syndrome antigen B (SSB) have a risk of 2–5% to associate fetal cardiac heart block during the first pregnancy, and 12–25% if previous pregnancies associated fetal cardiac heart block [13]. Data from a study that enrolled 33 pregnant women showed that the usage of hydroxychloroquine (HCQ) could contribute to the prevention of congenital heart block, its mechanism consists of inhibiting toll-like receptor signaling that has a role in the immune response [14]. Other treatment options include dexamethasone, a fluorinated steroid that diminishes maternal antibody levels, administered orally or intravenously, on a daily basis, until delivery [15]. Nonetheless, a multicenter, prospective, open-label clinical trial published in 2010 considered intravenous immunoglobulin (IVIG) as a potential therapy for cardiac heart block, 400 mg/kg every 3 weeks from 12–24 weeks of gestation having the ability to impede recurrence of cardiac heart block [16], while Ruffatti et al. noted in a 2011 report that a combined therapy that included plasmapheresis and intravenous immunoglobulin with a corticosteroid could convert second degree atrioventricular block to first degree atrioventricular block [17].

CONCLUSIONS

The existence of anti-SSA/Ro or anti-SSB/La antibodies during pregnancy imply a high risk of fetal cardiac impairment, while the development of fetal endocardial fibroelastosis plays an important role in altering ventricular diastolic function and ventricular disfunction progress in children and neonates. Pregnant women that associate a previous pregnancy affected by fetal cardiac heart block should be offered a particular antenatal care that includes fetal echocardiography monitoring from 16–18 to 28 weeks of gestation every two weeks. Proper treatment options should be considered from the moment of pregnancy confirmation until delivery. Extensive attention must be given to the intrapartum monitoring during labor, as this implies a difficult monitoring of atrial and ventricular fetal heart rate. Nonetheless, there are multiple antenatal treatment options such as hydroxychloroquine, dexamethasone, plasmapheresis or intravenous immunoglobulin.

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