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CLINICAL CASE OF NEONATAL LUPUS WITH CARTILAGINOUS METAPLASIA, FIBROSIS AND CALCIFICATION OF THE ATRIOVENTRICULAR NODE ZONE

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Neonatal lupus is a rare disease associated with the circulation in the mother's blood of one or more autoantibodies to soluble intracellular ribonucleoproteins Ro/SS-A and La/SS-B. This disease is extremely often manifested by congenital heart block, which can progress even after the birth of a child. We have described a case of fibrosis, calcification and cartilaginous metaplasia of the atrioventricular node zone, which caused complete atrioventricular block in a child who died from neonatal lupus.

Key words: neonatal lupus; atrioventricular block; cartilaginous metaplasia; fibrosis and calcification of the atrioventricular node; autoimmune lesion

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Rheumatic diseases (RDs) during pregnancy are associated with adverse outcomes for the health of both the mother and the fetus. Therefore, it is extremely important to address the issues of pregnancy planning and management, as well as postpartum period, in reproductive-aged patients with RDs. The effect of altered hormonal background during pregnancy on the mother's immune system is reflected in increased activity of T-helper 2 (Th2) cytokine profile, which includes interleukins 4, 10, and 13, that regulate humoral immunity. RDs that involve a Th2-dependent immune response include a group of diffuse connective tissue diseases (DCTDs), including systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome, among others. Potentiation of humoral immune response, leading to increased production of autoantibodies in these diseases, may explain the observed tendency for exacerbation of DCTDs during pregnancy and postpartum period [1].

The production of autoantibodies to soluble intracellular ribonucleoproteins Ro/SS-A (60 kDa and 52 kDa) or La/SS-B (48 kDa) is associated with the development of Sjogren's syndrome, but may also be observed in other DCTDs, including systemic sclerosis. Regardless of the type of underlying disease, the circulation of one or more of these autoantibodies in the mother's blood is associated with a serious complication for newborns - neonatal lupus erythematosus (NLE). After 6 weeks of gestation, placental formation is completed and autoantibodies (IgG class) begin to pass through the hemato-placental barrier into the fetal bloodstream. It is suggested that maternal anti-Ro/SS-A (especially 52 kDa) and anti-La/SS-B antibodies are capable of directly causing apoptosis of cells or provoking inflammation and subsequent fibrosis in target organs [2].

A 35-year-old woman with a history of three normal pregnancies resulting in urgent deliveries of healthy children has also been diagnosed with systemic scleroderma, limited form, generalized stage, with chronic skin involve-

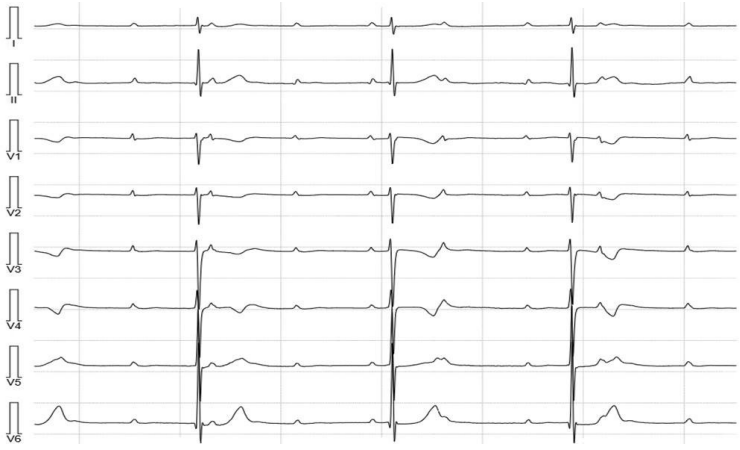

Fig. 1. Congenital complete atrioventricular block in a newborn.

ment (dense edema of the fingers in the past medical history), joint involvement (arthritis of the wrist joints), hematological disorders (leukopenia, thrombocytopenia in the past medical history), secondary Sjogren's syndrome (xerophthalmia, recurrent sialoadenitis), immunological phenomena (seropositivity for rheumatoid factor, antinuclear factor, anti-Ro/SS-A, anti-La/SS-B), with low disease activity.

The patient was admitted to the Perinatal Center of the Almazov National Medical Research Center for further examination and delivery. It is known that during pregnancy, there was an exacerbation of rheumatologic pathology, for which the patient received methylprednisolone and hydroxychloroquine (doses and duration of therapy are unknown). Later, the patient switched to maintenance therapy with methylprednisolone 4 mg and hydroxychloroquine 200 mg. During pregnancy, the patient had two acute respiratory viral infections. In the third trimester, the fetus was found to have bradycardia due to complete atrioventricular (AV) block.

During the mother's examination at the diagnostic center, mild iron deficiency anemia and second-degree disturbance of the fetal-placental blood flow were diagnosed. The fetus showed signs of heart failure (fetal hydrops) on the background of pronounced bradycardia, which led to an emergency Caesarean section at 35 weeks of gestation. At birth, the baby's condition was severe due to heart failure, AV block, morphofunctional immaturity, and prematurity, with a birth weight of 2100 g. Electrocardiography showed complete AV block with low ventricular contraction frequency (Fig. 1).

Echocardiography did not reveal any congenital heart defects. During the first few days after birth, there was an increase in signs of heart failure and metabolic disorders, and inotropic support was escalated due to the underlying complete congenital AV block. As conservative therapy was ineffective, urgent indications for temporary pacemaker implantation were established, followed by successful sequential pacing. However, ventricular fibrillation developed suddenly, which was refractory to medical therapy and cardioversion, and without the recovery of rhythm and independent hemodynamics. Extracorporeal membrane oxygenation (ECMO) via a neck cannula was initiated, and perfusion was provided by ECMO during resuscitation. Recurrent episodes of ventricular fibrillation were observed, and asystole occurred when attempting to disconnect the ECMO. Systemic hemodynamic disorders progressed and were resistant to therapy. Despite full resuscitation measures, a fatal outcome occurred.

During the autopsy of the child, no skin manifestations of NLE were found. Signs of acute heart failure were determined, such as ascites, anasarca, cerebral edema, and hydrothorax. The myocardium of all heart compartments was densely elastic in consistency. Attention was drawn to the pronounced compaction in the AV node with a dull, gray surface of the incision and indistinct boundaries.

Histological examination of autopsy material revealed multiple hemorrhagic necrosis of the liver, spleen, and myocardium. In the area of the AV node, a zone of extensive cartilaginous metaplasia, fibrosis, and calcinosis with subtotal replacement of the AV node was determined (Fig. 2). Thickening of the endocardium due to fibrosis and calcinates was observed in the zones of the left and right legs of the bundle of His, but Purkinje cells were locally preserved (Fig. 3).

To confirm possible transfer of maternal antibodies to the fetus through the placenta, immunohistochemical staining of the placenta was performed, which revealed weak diffuse expression of the C4d complement component on the syncytiotrophoblast in the external negative control, where C4d deposition occurs only on the fibrinoid of the placenta (Fig. 4). In the myocardium of the upper third of the interatrial septum, this marker was determined only on individual endotheliocytes of vessels (Fig. 2b).

DISCUSSION

C4d is considered a "footprint" of complement activation. Moreover, C4d is a widely accepted biomarker for antibody-mediated transplant rejection and plays a role in

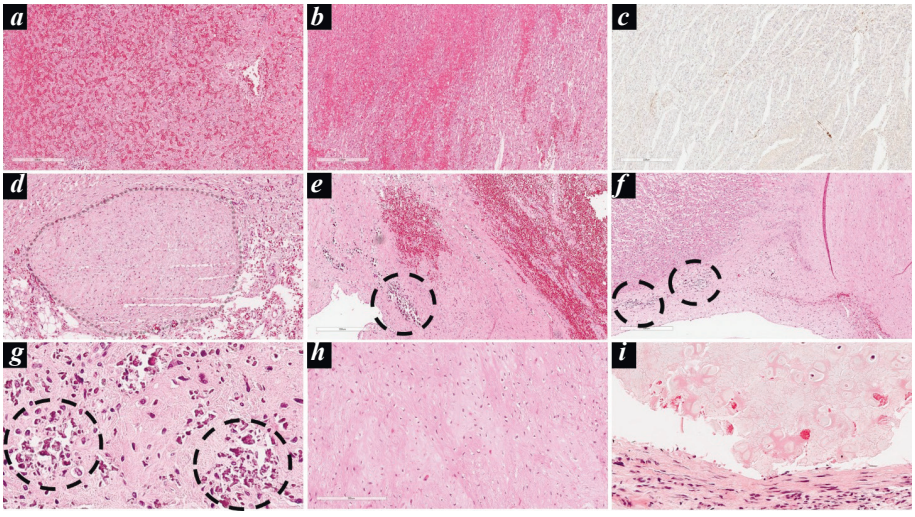

Fig. 2. Autopsy findings of the child: a, b - hemorrhages and hemorrhagic necrosis of the liver and myocardium, respectively (hematoxylin-eosin staining, x100); c - weak expression of C4d on the endothelium of individual vessels of the myocardium (brown staining, x100); d - marked fibrosis of the AV node zone (dashed line) with hemorrhages at the periphery (hematoxylin-eosin, x100); e - massive hemorrhages, fibrosis, and calcification (indicated by a dashed circle) in the AV node zone; f - marked fibrosis and calcification of the AV node zone (indicated by a dashed circle) with a focus of cartilaginous metaplasia (hematoxylin-eosin, x100); g - fibrosis and focal pinpoint calcification (indicated by dashed circles) in the AV node zone (hematoxylin-eosin, x400); h - cartilaginous metaplasia of the AV node zone (fibrous cartilage) - hematoxylin-eosin, x200; i - cartilaginous metaplasia of the AV node zone (paired chondrocytes with marked dystrophy) - hematoxylin-eosin, x200.

antibody-mediated pregnancy complications. Interestingly, placental C4d, detected in most cases of systemic lupus erythematosus and antiphospholipid syndrome, is diffusely expressed in the syncytiotrophoblast [3].

Clinically, NLE most commonly manifests with skin involvement (33.1%), liver (10.3%), blood (15.5%), and heart. The latter is usually represented by congenital heart block (CHB), occurring in more than half of NLE cases (62.5%). In this case, NLE may manifest as isolated CHB and in 95% of cases is the cause of this condition. While extracardiac manifestations of NLE usually resolve after elimination of autoantibodies from the newborn's bloodstream during the first 6 months of life, involvement of the cardiac conduction system is usually irreversible up to the development of complete atrioventricular block [4]. In the presence of SS-A/Ro and SS-B/La antibodies in the first pregnancy, the risk of developing CHB is 2-5%, but in subsequent pregnancies, the risk of recurrent NLE with rhythm disturbances increases to 20%. Signs of blockage can be detected from 16 weeks of pregnancy when the cardiac conduction system is formed and begins to function. Results of postmortem examinations of patients with autoantibody associated CHB demonstrate fibrosis and calcinosis of the AV node (in 16-25% of cases), bundle of His (in 14-20%), and its legs (in 56-68%), signs of inflammation in the form of infiltration of mononuclear cells, lymphocytes and histiocytes with deposition of antibodies and complement components, endocardial fibroelastosis, and moderate involvement of the contractile myocardium [5, 6]. In our case, there was also fibrosis and calcinosis of the AV node area and local fibrosis and calcinosis of the endocardium in the bundle of His legs, while no inflammatory infiltration was observed.

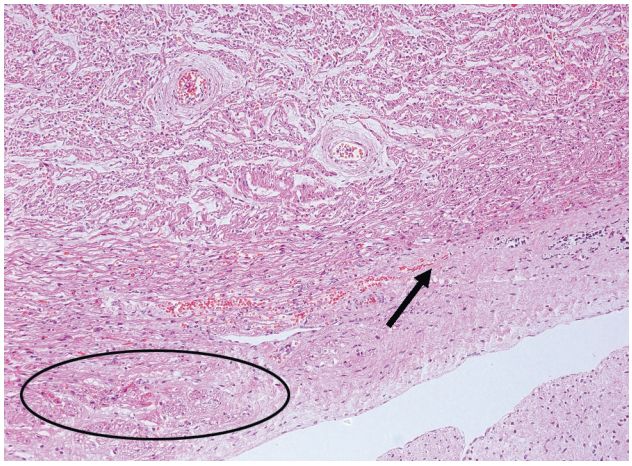

Fig. 3. Fragment of the interventricular septum with thickening due to fibrosis and calcifications of the endocardium (indicated by an arrow) and Purkinje cells in the left bundle branch (encircled by an oval); hematoxylin-eosin, x100.

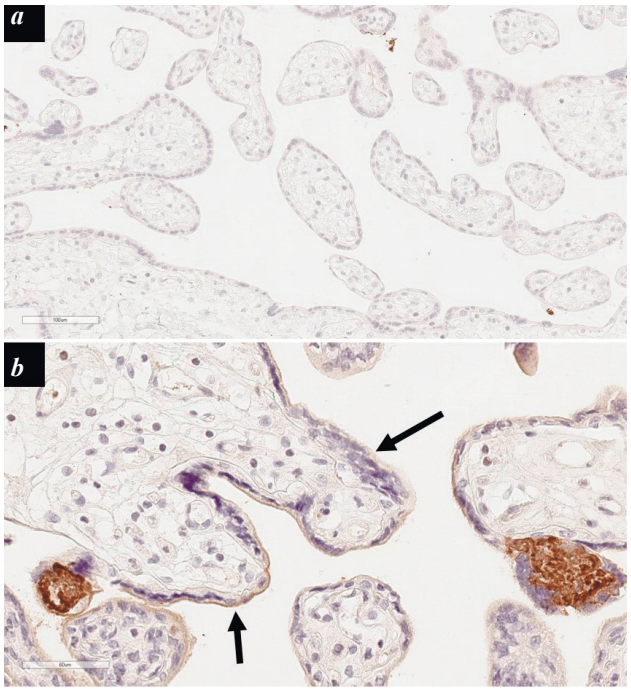

Fig. 4. Immunohistochemical staining of the placenta with C4d antibody: a - control placenta (x200), b - child's placenta (x400). Diffuse staining of syncytiotrophoblast (indicated by arrows) is notable.

A characteristic manifestation of NLE associated with autoantibodies is fibrosis, but the precise mechanism of tissue damage remains an area of intensive investigation. Many authors suggest that physiological apoptosis during fetal development may induce translocation of intracellular antigens to the cell surface, where they are then exposed to circulating antibodies. An alternative hypothesis is that maternal anti-Ro and anti-La autoantibodies bind to L-type calcium channels in fetal cardiomyocytes, inhibiting calcium influx, which ultimately leads to calcium dysregulation, calcium overload, and subsequent apoptosis.

Generation of apoptotic cardiomyocytes associated with antibodies (essentially immune complexes) activates macrophages with subsequent secretion of pro-inflammatory (tumor necrosis factor-alpha) and profibrotic factors. Regardless of the trigger of apoptosis, opsonization of apoptotic cardiomyocytes through toll-like receptors on macrophages is crucial for the inflammatory cascade that initiates replacement of the atrioventricular node and working myocardium with fibrous tissue [7].

Histological changes in the heart may be caused by the presence of pluripotent mesenchymal cells in the fibrous ring, which differentiate into fibroblasts, chondroblasts, and osteoblasts upon injury. However, it should be noted that the development of cartilaginous and especially bony metaplasia requires prolonged chronic exposure to damaging factors [8].

Intrauterine block associated with AV usually occurs in an intact heart and should be differentiated from secondary heart block with developmental defects, which is not associated with antibodies to SSA/Ro or anti-SSB/La. AV is often considered a model of passive acquired autoimmunity, in which antibodies are necessary but insufficient for the development of AV block, and fetal factors likely contribute. Detection of AV with heart involvement in fetuses usually occurs in utero between 17 and 24 weeks of pregnancy.

The degree of heart block includes all levels from first degree, detected incidentally on an electrocardiogram after birth or in utero by a prolonged PR interval, to third degree (complete) heart block, most commonly recognized. Complete AV block in these patients is irreversible. It has been

clearly documented that incomplete block (including those that are resolved in utero with dexamethasone) can progress after birth despite clearance of maternal autoantibodies from neonatal circulation. However, cases of complete resolution of a child from incomplete AV block have also been described [9].

Given all of the above, an important task becomes the prevention of fetal congenital heart block in patients with autoantibodies to SS-A/Ro and SS-B/La. Achieving remission or minimal disease activity of systemic autoimmune diseases according to the "treat-to-target" principle is a key factor in improving pregnancy and delivery outcomes for each individual disease. However, there is no clear data on the effectiveness of drug prophylaxis for neonatal lupus. Glucocorticoids have traditionally been used for this purpose based on general principles of managing systemic autoimmune diseases.

Non-fluorinated glucocorticoids (prednisolone, methylprednisolone) that can be used to control disease activity in pregnant women are not metabolized by the placenta and are unable to exert sufficient therapeutic effects on the fetus, making them unsuitable for treating neonatal lupus. While fluorinated glucocorticoids (betamethasone, dexamethasone) can penetrate the fetal bloodstream, recent meta-analyses have demonstrated their lack of significant impact on the incidence of congenital heart block. Based on the results of cohort studies, the European League Against Rheumatism recommends the use of hydroxychloroquine for neonatal lupus prophylaxis, primarily in cases where a previous pregnancy resulted in this complication.

REFERENCES

1. Østensen M, Villiger PM, Förger F. Interaction of pregnancy and autoimmune rheumatic disease. *Autoimmun Rev.* 2012;11(6-7): A437-46. https:// doi.org/10.1016/j.autrev.2011.11.013.
2. Clancy RM, Buyon JP. More to death than dying: apoptosis in the pathogenesis of SSA/Ro-SSB/La-associated congenital heart block. *Rheum Dis Clin North Am.* 2004;30(3):589-602. https://doi.org/10.1016/j.rdc.2004.04.013.
3. Sato Y, Yamaguchi T, Muraoka J, Taniguchi H, et al. C4d Deposition in Fetal Vessels of the Placenta in Neonatal Lupus Syndrome. *Case Rep Obstet Gynecol.* 2019;2019: 5863476. https://doi.org/10.1155/2019/5863476.
4. Capone C, Buyon JP, Friedman DM, et al. Cardiac manifestations of neonatal lupus: a review of autoantibody-associated congenital heart block and its impact in an adult population. *Cardiol Rev.* 2012;20(2): 72-6. https:// doi.org/10.1097/CRD.0b013e31823c808b.
5. Piercecchi-Marti MD, Mohamed H, Chau C, et al. Congenital atrioventricular block: Histological aspects. *Forensic Science International.* 2003;136(1-3): 12-15. https://doi.org/10.1016/s0379-0738(03)00224-x
6. Kovalev IA, Belozerov YuM, Sadykova DI, et al. Atrioventricular block in children. *Pediatricheskaya farmakologiya.* 2018;15(5): 365-375 (In Russ.) https://doi.org/10.15690/pf.v15i5.1959.
7. Tincani A, Rebaioli CB, Taglietti M, et al. Heart involvement in systemic lupus erythematosus, anti-phospholipid syndrome and neonatal lupus. *Rheumatology (Oxford)*. 2006;45 Suppl 4: iv8-13. https:// doi.org/10.1093/rheumatology/kel308
8. Carreon CK, Sanders SP, Ashworth MT. Chondroid and Osseous Metaplasia of the Central Fibrous Body in Adolescent Hearts with Mutations in TNNI3 and TNNT2 genes. *Pediatr Dev Pathol.* 2020;23(6): 453-460. https:// doi.org/10.1177/1093526620937572.
9. Buyon JP, Clancy RM. Neonatal lupus: review of proposed pathogenesis and clinical data from the US-based Research Registry for Neonatal Lupus. *Autoimmunity*. 2003;36(1): 41-50. https://doi.org/10.1080/08916930310 00067340.