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Review

Clinical and pathologic implications of extending the spectrum of maternal autoantibodies reactive with ribonucleoproteins associated with cutaneous and now cardiac neonatal lupus from SSA/Ro and SSB/La to U1RNP

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ABSTRACT

While the relationship between maternal connective tissue diseases and neonatal rashes was described in the 1960s and congenital heart block in the 1970s, the "culprit" antibody reactivity to the SSA/Ro-SSB/La ribonucleoprotein complex was not identified until the 1980s. However, studies have shown that approximately 10–15% of cases of congenital heart block are not exposed to anti-SSA/Ro-SSB/La. Whether those cases represent a different disease entity or whether another antibody is associated has yet to be determined. Moreover, the cutaneous manifestations of neonatal lupus have also been identified in infants exposed only to anti-U1RNP antibodies. In this review, we describe what we believe to be the first case of congenital heart block exposed to maternal anti-U1RNP antibodies absent anti-SSA/Ro-SSB/La. The clinical and pathologic characteristics of this fetus are compared to those typically seen associated with SSA/Ro and SSB/La. Current guidelines for fetal surveillance are reviewed and the potential impact conferred by this case is evaluated.

Contents

1. Introduction

Neonatal lupus (NL) represents a pathologic readout of passively acquired autoimmunity that was initially described in the 1960s

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(cutaneous) and 1970s (congenital heart block, CHB) [1,2]. The association of neonatal lupus with anti-SSA/Ro was identified in the 1980s [3]. Identification of in utero heart block in the absence of structural abnormalities predicts the presence of maternal autoantibody responses against the specific ribonucleoproteins SSA/Ro and/or SSB/La in >85% of cases [4]. However, that leaves approximately 15% of cases in which these maternal reactivities are not present, and whether those cases are "autoimmune" or represent a different clinical etiology remains unclear [4]. Prospective studies show the rate of developing CHB at approximately 2% in women with anti-SSA/Ro without a previously affected pregnancy, irrespective of maternal diagnosis [5–7]. The recurrence rate is increased by nearly tenfold in subsequent pregnancies [8]. Interestingly, one study evaluated the recurrence rate in CHB absent exposure to maternal anti-SSA/Ro and/or SSB/La and found no recurrences in 36 subsequent pregnancies [9].

With regard to incidence two population-based studies were performed irrespective of the presence of maternal autoantibodies. A study from Finland places the number at 1:17,000 live births with the highest annual estimates at 1:6500 [10]. A report from Stockholm County provided an incidence of anti-SSA/Ro autoantibody-related 2nd and 3rd degree block at 1:23,300 [11]. Although the signature cardiac disease typically manifests as CHB, which can be of varied degree but is most often complete [12], approximately 20% of affected offspring develop life-threatening cardiomyopathy [13,14], which can also present without associated CHB [12]. The case fatality rate is approximately 18% and approaches 50% with the development of a dilated cardiomyopathy or endocardial fibroelastosis [12].

Cutaneous manifestations of neonatal lupus have been reported with anti-U1RNP [15], and there has been a previously reported case of transient 1st degree block in a mother with SLE and anti-U1RNP antibodies absent anti-SSA/Ro antibodies [16]. However, antibody reactivity solely to U1RNP has never been detected in association with advanced block in a structurally normal heart. Here we report the first case of a neonate with CHB exposed to maternal anti-U1RNP antibodies absent anti-SSA/Ro-SSB/La.

2. Case report

A 40-year-old white female was diagnosed with mixed connective tissue disease (MCTD) at age fourteen when she presented with arthritis and Raynaud's syndrome. She was found to have a positive antinuclear antibody, low positive anti-Smith antibodies, and high titer antibodies to U1RNP. In addition to MCTD, she subsequently experienced a pulmonary embolus while on estrogen-containing birth control pills but did not have antibodies to cardiolipin, beta-2glycoprotein I, or the lupus anticoagulant. A genetic screen identified heterozygosity for one mutation, G20210A, in prothrombin, homozygosity for the *MTHFR* gene C677T mutation, and homozygosity for plasminogen activity inhibitor-1 4G/5G. She had one previous pregnancy in 2011, which resulted in the birth of a healthy girl at term by vaginal delivery. Prior to and during that pregnancy she consistently tested negative for anti-SSA/Ro and anti-SSB/La antibodies. She conceived again in 2015, and anti-SSA/Ro and anti-SSB/La antibodies remained undetectable. Medications continued during pregnancy were enoxaparin 40 mg sc daily and aspirin 81 mg daily. A routine obstetrical sonogram at 28 weeks revealed a fetal heart rate in the 130 s. However, during the next scheduled visit at 30 2/7 weeks the fetal heart rate was noted to be in the 50s, and a sonogram confirmed bradycardia. A female child weighing three pounds and twelve ounces was delivered by emergency C-section with APGAR scores of 4 and 7 at 1 and 5 min, respectively. An electrocardiogram revealed complete (3rd degree) heart block. The child was initially placed on nasal CPAP and subsequently intubated, given isoproterenol, and transferred to a local level IV neonatal intensive care unit. Rapid deterioration ensued with respiratory distress syndrome and signs of pulmonary hypertension. She was given poractant alfa and started on an oscillator with inhaled nitric oxide (iNO). Epinephrine was started in lieu of isoproterenol but discontinued due to multiple premature ventricular contractions/trigeminy, and dopamine was started. Broad-spectrum antibiotics (ampicillin and ceftriaxone) were initiated in addition to hydrocortisone for hemodynamic support. An echocardiogram on the first day of life showed a moderately dilated left ventricle with moderately decreased biventricular systolic dysfunction. There was no pericardial effusion. There was a small patent ductus arteriosus with a trivial left-to-right shunt. Repeat echocardiogram on day 4 showed improved left ventricular systolic function and right-sided function was within the lower limits of normal. An epicardial pacemaker was placed on day 5 and set to VV1 90, and patent ductus arterial ligation performed on day 12. The hospital course was complicated by concern for necrotizing enterocolitis, which was managed conservatively; a non-occlusive aortic thrombus that extended inferiorly from the renal vessels presumed secondary to an umbilical venous line; a transverse sinus thrombosis, which raised the possibility of a hypercoagulable state; a right grade 1 and left grade 2 interventricular hemorrhage; cholestasis; and renal failure with anasarca requiring peritoneal dialysis. Care was withdrawn at day 28 for hypotension despite maximum vasopressor support and broad-spectrum antibiotics. An autopsy was performed.

2.1. Autopsy

A limited postmortem examination was performed. The autopsy revealed severe anasarca, pleural effusions, and pulmonary findings consistent with immaturity. The heart was structurally normal but enlarged (22.7 g, normal range 12.4 ± 2.8 g). Initial dissection of the heart was done along the lines of blood flow, and additional dissection was performed to obtain the AV node and adjacent conducting system for histologic analysis. Histologically, there was loss and calcification of the myocytes in the area of the bundle of His and extending into the proximal Purkinje fibers (Fig. 1A,B). The AV node was not involved in the destructive process (Fig. 1C). Areas of early myocyte calcification were seen in the septal myocardium likely related to a secondary process during the time of cardiac support (Fig. 1D).

Maternal blood was sent to the Research Registry for Neonatal Lupus at New York University School of Medicine for evaluation of antibodies specific for 60 kD SSA/Ro (native protein), 52 kD SSA/Ro (recombinant protein), and 48 kD SSB/La (recombinant protein) as previously described [17] and were found to be negative, Table 1. Anti-U1A of the

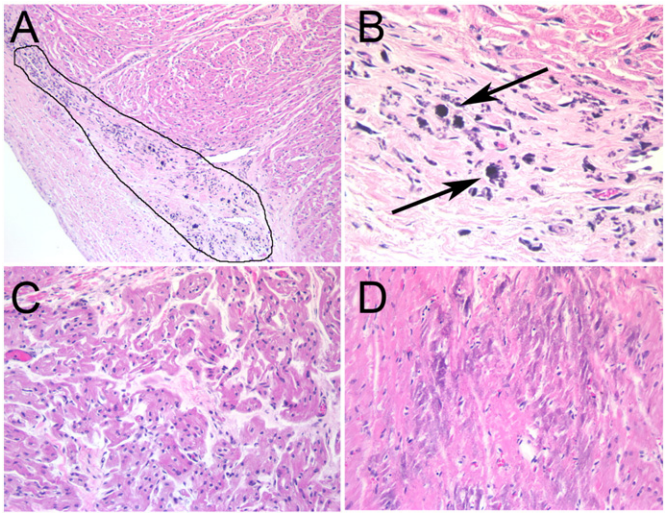

Fig. 1. A – Low-power view of the bundle of His (circled) demonstrating myocyte loss, scarring and calcification confined to the conducting system (100× original magnification, hematoxylin & eosin). B – Higher-power view of the conducting system showing calcified remnants of myocytes (arrows) and dense collagen (200×, H&E) C – High-power view of the AV nodal tissue showing no evidence of pathology in this location (200× H&E). D – Focal areas of myocyte calcification of the non-conducting septal myocardium were appreciated (200×, H&E).