Anti-Ro (SSA) Antibody in Pregnancy

Case Presentation

A 28 year old G4P1Ab2 white female presented at 12 weeks gestation for a routine prenatal evaluation. Her past medical history was significant for marked photosensitive dermatitis and occasional polyarythralgias since the age of 18. Her past obstetrical history was remarkable for 2 spontaneous abortions, and for a 2 year old asymptomatic son with complete congenital heart block. There was no family history of any connective tissue disease. Physical exam was normal except for an erythematosus firm maculopapular rash on areas of the body exposed to light. Routine laboratory tests revealed no abnormalities, and an anti-nuclear antibody (ANA) test was negative. An anti-Ro (anti-SSA) antibody level was requested.

What is anti-Ro antibody?

The anti-Ro antibody takes its name from the first two letters of the patient in whom it was first found. She suffered from arthritis, pleuropericardial disease, and SLE (systemic lupus erythematosus) type skin lesions (1). She did not have demonstrable antinuclear antibodies. It has subsequently become apparent that a particular disease pattern - termed subacute cutaneous LE and consisting of prominent photosensitivity with or without associated renal damage - is common in ANA-negative patients who have anti-Ro antibody. This disease pattern has also been called ANA-negative SLE.

At this same time, anti-SSA antibodies were described in patients with Sjogren's syndrome or the sicca complex. It has since been demonstrated that the SS-A and Ro antigens are immunologically identical, and the antibody is now referred to as anti-Ro (SSA) antibody.

The Ro(SSA) antigen is a small ribonucleoprotein (RNP) complex present predominantly in the cytoplasm (2), but also thought to be present in the nucleus (3). The RNA associated with the Ro(SSA) antigen is not related to messenger, nucleolar or transport RNA and the associated protein(s) are not histones. Although the function of the Ro antigen is unknown, it has been postulated to play a role in converting nuclear RNA precursors to mature cytoplasmic ribosomes (4,5).

Detection of anti-Ro(SSA) antibody utilizes gel double immunodiffusion in 0.6% agerose with saline extracts of human spleen or calf thymus as the source of Ro(SSA) antigen.

Anti-Ro(SSA) antibody is present in the serum of 60-70% of patients with Sjogren's syndrome, 25-35% of patients with SLE, and 0.1% of patients without evidence of connective tissue disease (4,6).
The negative ANA test in many anti-Ro(SSA) antibody-positive woman has been explained in several ways. Alexander and Provost (4) have suggested that the false negative ANA tests are due to the substrates used for detection. Mouse liver cells, used as the standard substrate for many years, had a false negative rate of 5-10% in their series. Scott (5) blamed the false-negative ANA on the solubility or lability of the Ro antigen in certain fixatives. In addition, Scott also recommended using cells with large nuclei (e.g., cultured cells) to increase the sensitivity of the ANA test. Tan (7) observed that the Ro antigen is present in low concentrations in certain cell types, and that testing of the same ANA-negative sera on multiple substrates increased the detection of antinuclear antibodies.

Significance of anti-Ro(SSA) in the pregnant woman

A number of studies have linked the presence of anti-Ro(SSA) antibody during pregnancy with the subsequent delivery of a child with isolated congenital complete heart block (CCHB). Isolated congenital complete heart block is a rare event, occurring at a rate of 1/20,000 live born infants (8). The pathogenesis of this lesion is not known, although it is most often associated with congenital anatomic anomalies of the heart; it is also a common consequence of the heart surgery necessary to repair such congenital defect(s).

The incidence of isolated CCHB in the children of women with SLE is not known, but it is well appreciated that these women suffer a higher frequency of fetal wastage and neonatal complications. It has been proposed that transplacental passage of antibody from mothers with SLE may result in degeneration and fibrosis of the fetal cardiac conduction system. If an affected child survives infancy, the clinical course is relatively favorable; the majority of these children are usually asymptomatic, and a lifespan of at least 40 years is to be expected. The most common cause of death in these children is Stokes-Adams attacks.

The correlation between maternal connective tissue disease and fetal CCHB was investigated by McCue et al. (9). Twenty-four children with CCHB and their 23 mothers were carefully analyzed for evidence of connective tissue disease. Although laboratory evaluation included testing for ANA and rheumatoid factor, testing for anti-Ro(SSA) antibodies was not done. Seven of the mothers had overt clinical signs of SLE, and 4 additional mothers had laboratory evidence (i.e., positive ANA or rheumatoid factor test) of connective tissue disease. However, 8 of the mothers had neither clinical nor laboratory evidence of any connective tissue disease. The remaining 4 mothers were lost to follow-up. Of the children born to symptomatic mothers, only 5/14 had isolated CCHB as the sole defect, a frequency which is not significantly different from the 3/8 children with isolated CCHB born to women lacking clinical or laboratory evidence of connective tissue disease. The remaining children in this study had various anatomic cardiac lesions in addition to CCHB.

Chameides et al. (10) presented six cases of children born with CCHB. Although three of the six children had isolated CCHB, the remaining three had evidence of additional congenital heart lesions (two patent ductus arteriosus, and one atrial septal defect and a dysplastic pulmonary valve). Four of the six mothers had florid symptoms of SLE during pregnancy, and the remaining two mothers developed overt
signs of SLE within 2 years after the birth of the afflicted child. Three of the mothers had particularly severe disease, and subsequently died of renal damage associated with SLE.

Paredes et al. (11) presented a case report of a woman symptomatic with primary Sjogren's syndrome, who was delivered of a child with isolated CCHB. The mother had an ANA titer of 1:80, but no anti-Ro(SSA) antibody was detected.

Scott et al. (12) produced the most convincing evidence to date linking maternal autoantibodies to the occurrence of isolated CCHB. They analyzed mothers and children with a variety of cardiac abnormalities, and found serologic evidence of connective tissue disease only in the mothers of the children born isolated CCHB. Of 41 such mothers, 34 had anti-Ro(SSA) antibody, but only 16 were ANA-positive. All the symptomatic mothers and 18/24 asymptomatic mothers were anti-Ro(SSA) positive. ANA tests were positive in only 11/17 symptomatic mothers and 5/24 asymptomatic mothers. Most importantly, 4 of the 17 subsequent offspring of those mothers who were anti-Ro(SSA) positive had isolated CCHB.

Unfortunately, the anti-Ro(SSA) antibody status of normal pregnant women is not well defined (13). Harmon et al. (14) analyzed the sera of 461 apparently normal pregnant women for the presence of anti-Ro(SSA) antibodies and obtained four positive results (approximately 1%). These 4 mothers were all clinically healthy, and none of their infants had neonatal lupus or congenital heart block.

In addition to the link with isolated CCHB, maternal anti-Ro(SSA) antibodies have been implicated in fetal wastage. Cowchock et al. (15) investigated the frequency of anti-Ro(SSA) antibodies in 12 of a group of 14 women with unexplained abortions (i.e., those not attributable to uterine abnormalities, parental chromosome translocation, or luteal phase defects). None of the 12 demonstrated anti-Ro(SSA). The only significant difference between the group with unexplained abortion and the control group was a higher incidence of positive ANA tests in the former (4/14) versus the latter (1/16).

In the case presented here, the patient's symptoms argue strongly for the existence of connective tissue disease, and her negative ANA test does not rule out this possibility. If anti-Ro(SSA) antibody is detectable in this patient's serum, then her unborn child will be at an increased risk of being born with isolated CCHB. In addition, her previous 2 spontaneous abortions might result from a previously undiagnosed connective tissue disease.

The use of the anti-Ro(SSA) antibody test to screen all asymptomatic pregnant women cannot be justified. Although the test has a calculated sensitivity of 83% (12) and specificity of 99% (14), the prevalence of CCHB is so low (1/20,000 births) that the test has a positive predictive value of only 0.4%. The negative predictive value, however, is 99.9%. Thus for every 250 screened women found to have anti-Ro(SSA) and going to term, only one would have a child with CCHB. We do not know how to distinguish that one woman from the other 249 asymptomatic pregnant women who also have anti-Ro(SSA) antibodies. On the other hand, for a woman who has had one previous child afflicted with isolated CCHB, a positive anti-Ro(SSA) antibody test would give her a 24% chance of having a second afflicted child.
Therefore, this test would be most appropriate for that population of pregnant women who have a history of multiple spontaneous abortions. Unfortunately, there have been no studies looking at the incidence of anti-Ro(SSA) antibody in habitual aborters, and therefore the test cannot be interpreted with any degree of confidence in the population for whom it would be most useful.

References


