Spontaneous Formation of an Anti-S Alloantibody in Association with Mixed Connective Tissue Disease*

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ABSTRACT

A spontaneous anti-S alloantibody developed without prior transfusion in a 33-year-old male with mixed connective tissue disease. It was detectable by indirect antiglobulin testing using anti-IgG specific, as well as polyspecific anti-human globulin. All previously reported naturally occurring anti-S antibodies had been cold reactive agglutinins, presumably IgMs.

Introduction

Anti-S is almost exclusively encountered as an alloantibody formed following transfusion or as a consequence of pregnancy. The exceptions noted in the literature have been limited to four case reports. In two of these cases, auto-anti-S antibody production resulted in an autoimmune hemolytic anemia. In the other two, the anti-S activity was not felt to be of clinical significance. In all four of these cases, the anti-S antibodies have been cold reactive agglutinins, presumably IgMs. This report documents for the first time the spontaneous formation of an IgG anti-S alloantibody in a patient with mixed connective tissue disease and endocarditis.

Case Report

A 33-year-old white male agricultural worker was hospitalized 10/13/85 at the Medical University Hospital with progressive dyspnea. Relevant past history included a spontaneous right vitreous hemorrhage coincident with a 30,000 per µl platelet count. Studies performed at that time included a positive speckled antinuclear antibody (ANA) at a titer of 60, positive anti-ribonucleoprotein (RNP) at a titer of 16,000, a normal prothrombin time, but prolonged partial thromboplastin time. He was treated with prednisone with a rise in his platelet count to 69,000 per µl and remained asymptomatic on 10 mg prednisone per day until the onset of his current symptoms. He had never received blood or blood products.

Echocardiography performed on this admission, revealed a large subvalvular mass that protruded into the aortic orifice in systole. Laboratory studies included a WBC of 6500 per mm³ with a normal differential; Hgb of 9.3 g per dl; reticulocyte count of 102,000 per mm³; platelets 59,000 per mm³; prothrombin time 13.1 secs (control 13.0 secs.); partial thromboplastin time 42.8 secs (control 30 secs): a positive dilute thromboplastin test indicative of a "lupus anticoagulant"; serum positive for the presence of IgG anti-platelet antibodies; ANA positive at a titer of 40 in a speckled pattern; double stranded deoxyribonucleic acid (DNA) positive at a titer of 40 and negative rheumatoid factor. Results of the

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immuno-hematology evaluation appear in the Results section. Seven sets of blood cultures demonstrated no growth. The patient was thought to have mixed connective tissue disease and endocarditis. Treatment with vancomycin and gentamicin, furosemide and prednisone (20 mg q 6 hr) resulted in marked clinical improvement.

The patient was readmitted two weeks later for aortic valve replacement. Prior to cardiac surgery, he received, on each of five consecutive days, 30 g infusions of immunoglobulin concentrate in an unsuccessful attempt to increase his platelet above 30,000 per mm³. Following the last immunoglobulin infusion, he received 370 cc of single donor red cell free-platelet concentrate. The platelet donor was typed as O Rh Negative, positive for s, N, U, and negative S and M. He underwent successful aortic valve replacement using 15 S-negative red cell units for transfusion; however, he gradually deteriorated over a month and died of progressive hypoxia and pulmonary hemorrhage. The aortic valve removed from our patient showed fibrosis, focal necrosis and intense acute inflammation, but no bacteria or fungi were seen histologically. Cultures obtained from valve tissue yielded no growth.

Methods

Antibody specificity, direct and indirect antiglobulin testing, and red cell phenotypes were determined by standard laboratory technique using commercial red cell test panels,*†‡ selected cells,§§ anti-human serum§ and anti-IgG* and red cell typing sera.*§ Red cell heat elution was performed by the method of Landsteiner and Miller.5 Serum antiplatelet antibodies were determined by incubating donor platelets with patient serum followed by fluorescein-conjugated anti-human IgG, with the resulting immune complex measured using flow cytometric analysis.6

Red cell free platelet concentrate was obtained by cytapheresis using a dual stage blood separation channel on the IBM 2997 Blood Cell Separator at a centrifuge speed of 2400 RMP. The immuno-globulin administered intravenously was Gamimmune five percent†.

Results

The patient’s blood type was O Rh positive. A two cell antibody screen had very weak positivity to one screening cell, but antigen specificity could not be determined. His direct antiglobulin test was weakly positive using rabbit anti-human serum as well as anti-IgG specific or anti-C3 antiserum. A red cell heat eluate demonstrated no antibody.

Ten days following his initial course of prednisone and antibiotic therapy, his direct anti-globulin test was negative, but a ± (to heterozygous ss cells) or 1 + (to homozygous SS cells) anti-S was demonstrated by indirect antiglobulin testing by using anti-human serum. Testing was noted to be stronger in albumin than saline. Homozygous S cells tested at room temperature and at 37° in saline or at 37° in albumin were not agglutinated by immediate spin testing. The patient’s red cells were phenotyped positive for M, s, and V and negative for N and S. Testing performed three weeks later at the time of admission for aortic valve replacement showed his direct anti-globulin test to have remained negative and the anti-S reactivity to be unchanged in strength. All 15 S-negative units tested against the patient’s serum samples at this time were found to be compatible through crossmatch testing.

Discussion

The formation of autologous red cell antibodies in individuals with collagen vascular disease is not uncommon. Approximately 15 percent of patients with systemic lupus erythematosus have a positive direct antiglobulin test.7 How-
ever, the formation of an unstimulated "natural" alloantibody is rare, occurring mainly as IgM antibodies having ABO, I, Lewis, P1 and occasionally MN system specificities; these IgM agglutinins are presumably made in response to various environmental lectins or micro-organism antigens and crossreact with similar or identical red cell antigens. All previously reported patients with spontaneous anti-S alloantibody have had cold reactive, agglutinating IgM antibodies. Our patient's spontaneous production of a warm reactive, IgG anti-S antibody appears to be the first such report.

The naturally occurring anti-S reported by Constantoulis had a "complete", saline agglutinating antibody reacting optimally at 4°C, but only weakly and not with all S-positive cells at 37°C. The case of Coombs also demonstrated an antibody reacting more strongly at room temperature than at 37°C. Both Coombs' patient and ours developed anti-S in a clinical setting of chronic or subacute endocarditis suggesting the possibility of crossreactivity by the antibody directed primarily towards a bacterial antigen. However, an organism was not identified in either of our cases. That both patients developed alloantibodies as a manifestation of underlying autoimmune disease is a more appealing explanation. This interpretation, particularly in our patient, is consistent with his other multiple serologic abnormalities including a lupus anticoagulant, platelet antibody, positive nuclear antibodies. The two cases of auto-anti-S mentioned in the introduction, likewise had evidence of other immune phenomena. The finding of spontaneous anti-S reactivity, whether it be owing to an alloantibody or an autoantibody, should alert the clinician to the possibility of an underlying autoimmune disease state.

References