

Case 17

M.B. is a 47 year-old woman who developed a sun sensitive rash (Fig. 1) and polyarthritis at age 19 years. Laboratory tests showed pancytopenia (her WBC was $2.3 \times 10^9/l$), Hct 21% (normal $> 36\%$), and platelets 120,000 ($\times 10^6/l$; normal $> 150,000$). Her serum creatinine was 1.1 mg/dl (high normal). She had a biological false positive test for syphilis, an elevated APTT (an indicator of clotting capacity) of 45 sec, a positive Coombs test (an indicator of autoantibodies against RBCs), positive anti-nuclear antibodies (ANA) in a “rim” pattern (Fig. 2), elevated anti-DNA antibody, and low serum complement. Shortly thereafter she developed fever and was admitted to the hospital. Blood cultures were positive for *Neisseria meningitidis*. She was treated with intravenous Ceftriaxone (a cephalosporin), started on high dose corticosteroids, and transfused with packed red blood cells. A kidney biopsy showed Class II lupus nephritis (mesangial immune deposits only). She improved on IV antibiotics and was discharged from the hospital on oral prednisone.



Fig. 1. Malar rash in M.B. at age 19.

She did relatively well over the next 8 years on low dose steroids with normal laboratory values except for a persistently prolonged APTT. She became pregnant. At 36 weeks gestation she developed ecchymoses (bruises), edema, and hypertension. A platelet count was 77,000; she had

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an active urinary sediment (presence of casts) and 2 grams of proteinuria. An emergency C-

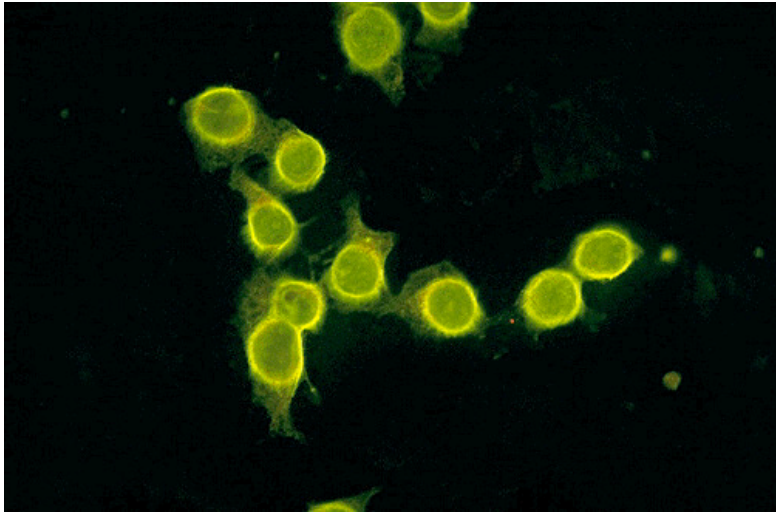


Fig. 2. ANA prep with a “rim” pattern, almost diagnostic of SLE. This test is performed using the patient’s serum and a cultured cell line; antibodies against nuclear antigens are detected following addition of a fluorescently-conjugated antibody against human IgG. Stained cells are visualized using fluorescence microscopy.

section was performed delivering a healthy baby boy. Ten hours post-partum she had a generalized seizure and a CT scan of the brain showed a right parietal infarct. Additional laboratory tests showed elevated anti-DNA antibodies, the presence of autoantibodies to Sm (Smith antigen), evidence of hemolytic anemia with a hematocrit of 19% and reticulocyte count of 20% (increased, suggestive of hemolysis), and a creatinine of 2.6 mg/dl. Renal biopsy showed Class IV lupus nephritis (diffuse proliferative lupus nephritis with subendothelial immune deposits and crescents). She was treated with high dose steroids and cyclophosphamide. Her blood counts gradually normalized, she recovered fully from her stroke, and her renal function improved to a serum creatinine of 1.3 mg/dl. Her steroids were gradually tapered to low doses, cyclophosphamide was discontinued and she did well over the next several years.

At the age of 37 she was admitted following an episode of exertional chest pressure radiating to the neck and right shoulder. An ECG showed anterior T wave inversions (evidence of myocardial ischemia). Anti-DNA and complement levels were normal, but anti-cardiolipin antibodies were markedly positive. Cardiac catheterization showed occlusion of the left anterior descending artery and the patient underwent percutaneous transluminal angioplasty. She was discharged on Warfarin (Coumadin; a blood thinner).

Questions for Case 17

- (1) Describe the immunologic mechanisms in this patient that caused:
 - a. thrombocytopenia
 - b. anemia
 - c. renal disease
 - d. prolonged APTT and biological false positive test for syphilis
 - e. susceptibility to infection with *N. meningitidis*

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- (2) Studies have shown the presence in SLE patients of autoreactive CD4⁺ T cells that respond to histone peptides and promote production of anti-DNA antibodies *in vitro*. How might anti-histone CD4⁺ T cells specifically provide help to anti-DNA B cells?
- (3) What role are complement proteins thought to have in the pathogenesis of SLE? What role do immune complexes play in SLE and how might they contribute to glomerulonephritis in this patient?
- (4) What genetic factors are thought to predispose to SLE?
- (5) Of the various for autoantibodies currently available, which are the most specific for SLE?
- (6) M.B. had several episodes of vascular occlusion that resulted in a stroke and a myocardial infarction. What are possible mechanisms in this patient that might account for these episodes? How is these related to the prolonged APTT and the biological false positive test for syphilis?
- (7) Many autoantibodies in SLE display extensive somatic hypermutation. What does this say about negative selection in SLE?
- (8) Polymorphisms of FcγRIIB, the ITIM-bearing receptor, are associated with autoimmunity. Would you predict that these polymorphisms encode proteins with loss-of-function or gain-of-function (with respect to FcγRIIB)? What does this say about the pathogenesis of autoimmunity associated with these polymorphisms?