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Warren L. Kupin

Maria Sawdyk

Anti-HLA Antibodies Complicating Infectious Mononucleosis with Thrombocytopenia and Neutropenia

Warren L. Kupin, MD,* and Maria Sawdyk, MD†

A case concerning a 21-year-old male college student with thrombocytopenia and neutropenia complicating infectious mononucleosis is presented. Although the patient had no prior history of alloimmunization, a broad spectrum anti-HLA antibody was strongly positive in his serum. Concomitant with resolution of the hematologic abnormalities, the titer of the antibody diminished. This case is unique both in the severity of the thrombocytopenia and neutropenia and for the circulating HLA antibody most likely of viral origin. (Henry Ford Hosp Med J 1986;34:65-7)

Infectious mononucleosis has been associated with a wide variety of hematologic manifestations, of which the production of a marked atypical lymphocytosis is most characteristic. Mild subclinical thrombocytopenia (60/mm^3 to 140,000/mm^3) and neutropenia (1,000/mm^3 to 1,800/mm^3) have been found to occur in upwards of 24% to 50% of the cases (1,2). Severe thrombocytopenic purpura (20,000/mm^3) and an absolute neutropenia (750/mm^3) are each considered to be extremely rare manifestations of infectious mononucleosis and occur in less than 1% and 2% of the cases, respectively (3,4). Recent studies strongly implicate an autoimmune basis for the severe thrombocytopenia, while no one explanation has yet been accepted for the absolute neutropenia (5). We report a case of infectious mononucleosis combining both of these uncommon hematologic disorders associated with the presence of a broad spectrum circulating anti-HLA antibody.

Case Report

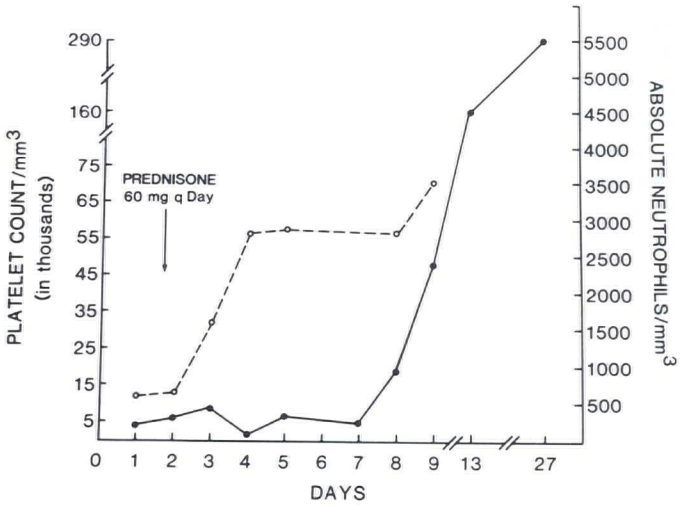
A previously healthy 21-year-old male college student, referred from an outside hospital, complained of spontaneous bleeding from his gums and easy bruising over a two-day period. He had been well until three weeks prior to his presentation when he developed a sore throat, low-grade fever, and tender cervical adenopathy. Subsequently, he had experienced persistent malaise and anorexia resulting in a weight loss of 15 pounds. He was not on any medications, had no toxin exposure, and no concurrent medical problems.

Physical examination revealed a thin but muscular male in no acute distress. Vital signs were normal. Multiple purpuric lesions were noted on his thighs and buttocks with petechiae over the dorsum of his feet and on his shoulders. Hemorrhagic bullae were noted on the buccal mucosa and palatine petechiae were present. Diffuse nontender adenopathy was palpable. Splenomegaly was measured to 11 cm by percussion. Stool was trace Hemoccult positive.

Laboratory data revealed a white cell count of 8,000/mm^3 with 4% mature neutrophils, 4% bands, and 46% atypical lymphocytes. The initial platelet count was 4,000/mm^3 but fell to a low of 2,000/mm^3 during hospitalization. Hemoglobin was 12.6 g/100 mL with a reticulocyte count of 1.5%. Westergreen sedimentation rate was 10 mm/h. Liver function tests revealed mild transaminase elevation. Coombs' test was positive for an IgM cold agglutinin of anti-i and anti-I specificity. Immune electrophoresis revealed diffuse mild hypergammaglobulinemia. Urinalysis showed 5 to 10 RBC/HPF.

Bone marrow examination on the day of admission revealed megakaryocyte hyperplasia with mild granulocyte hyperplasia. Subsequent monospot test was positive; cold agglutinin titer was 1:32; and heterophile antibody titer was 896 before absorption with guinea pig kidney cells, 448 afterward, and 28 after absorption of beef cells. Epstein-Barr virus titer was 10,240 initially and 2,560 after two months.

The patient was started on 60 mg/d of prednisone the evening of admission. The course of the platelet and WBC levels are depicted in the Figure. Mild bloody diarrhea developed on the seventh day, but all



Figure—The patient's platelet (•—•) and neutrophil (○—○) counts during hospitalization and after discharge.

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*Fellow, Department of Internal Medicine, Henry Ford Hospital. Currently Staff Physician, Nephrology Division, Henry Ford Hospital.
†Department of Internal Medicine, Division of Hematology, Henry Ford Hospital.
Address correspondence to Dr Sawdyk, Division of Hematology, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202.

bleeding manifestations stopped by the next day, and the patient was discharged on the tenth day with a slowly tapering dose of prednisone. At one- and two-month follow-up he was off all steroids and doing well with a normal platelet count.

An antiplatelet antibody test (method of Lizak and Grumet [6]) on admission was negative in the complement mediated cytotoxicity assay, but the patient's serum was strongly positive for anti-HLA antibodies. Two months later his anti-HLA antibody was still present but in lower titer (measured by percent kill of lymphocytes), with 100% cell kill on admission decreasing to 50% to 60% cell death at the time of follow-up.

Discussion

We have reviewed the 53 cases of thrombocytopenic purpura secondary to infectious mononucleosis that have been reported thus far in the English literature. In addition to our own case, only 12 well-documented cases of thrombocytopenia of less than 5,000/mm^3 have been reported (5,7-12). In light of the frequent finding of megakaryocyte hyperplasia (72% of the cases) in these thrombocytopenic patients, an autoimmune mechanism has long been postulated (13).

Numerous techniques have been successfully and unsuccessfully employed to determine the existence of an antiplatelet antibody. In 1972, Ellman showed the presence of a platelet-bound IgG antibody utilizing a C^{14}-serotonin release assay, which has been recently confirmed (5,14). The mechanism of platelet destruction has been compared to that in idiopathic thrombocytopenic purpura involving predominantly splenic reticuloendothelial removal of antibody-coated platelets without complement activation. No specific platelet antigen has yet been implicated as a site for antibody binding.

Mild absolute neutropenia (2,865/mm^3) in the first three to four weeks of illness was noted by Cantow (2) in 80% of the cases. Absolute counts were rarely below 1,000 and occurred without clinical sequela. Recently, however, Hammond reviewed 11 cases of severe neutropenia (200/mm^3) reported in the literature and found two episodes of related sepsis, one due to *Staphylococcus aureus* and one secondary to *Hemophilus influenza* and *Staphylococcus aureus* (15).

Bone marrow examinations in these patients with severe neutropenia revealed four cases of myeloid hyperplasia and seven cases of "maturation arrest" at the promyelocyte level. A further review of nine prospective cases of mild neutropenia revealed myeloid hyperplasia in all patients (13). Megakaryocyte cell lines were normal, and no case involved concomitant thrombocytopenia.

Leukoagglutinating activity has been noted in the sera of patients with infectious mononucleosis, and circulating anti-neutrophil IgG antibody has been recently demonstrated (4,16). Consequently, the pathogenesis of neutropenia, in conjunction with thrombocytopenia in infectious mononucleosis, appears to be clearly linked to an autoimmune mechanism.

Combined autoimmune thrombocytopenia and neutropenia have been found in different clinical settings: systemic lupus erythematosus, idiopathic Felty's syndrome, and immune hemolytic anemia (17). Platelet antibodies have been defined with varying antigenic specificities including anti-ABO, anti-PI^{A1}, anti-HLA, and drug related and ITP related antibodies. Our patient exhibited severe thrombocytopenia (2,000/mm^3) and neutropenia (640/mm^3) associated with active Epstein-Barr virus infection that resolved over a two-week period with prednisone therapy. An HLA-antibody was detected both during the acute disease and two months later during convalescence in decreasing titer.

Specific HLA typing of the antibody was unsuccessful because lymphocytoxicity occurred in all wells of the tissue-typing tray. This illustrates the unique broad spectrum of this HLA antibody in an individual with no prior history of transfusions of blood or blood products. In the absence of alloimmunization, we can only speculate as to its etiology in our patient.

The specificity of this antibody must be directed against class I HLA antigens of the A, B, and C systems since platelets have not been shown to express class II antigens of the HLA-D locus. Antigenicity is genetically determined on chromosome #6 and expressed by the heavy chain of the HLA complex, while the B_2 microglobulin glycoprotein is coded for separately on chromosome #15. Due to the broad specificity of this antibody, involvement of the ubiquitous B_2 microglobulin component seems most likely. To fulfill this hypothesis, the Epstein-Barr virus, through its binding to specific E-B virus receptors known to be present on B lymphocytes, must alter the HLA complex. Indeed, a physical link between the receptor for E-B virus and a major histocompatibility complex glycoprotein has been demonstrated, and the cytotoxic T-cell response to this viral infection has been shown to be dependent on the presence of the HLA complex (18,19).

Our patient's antiplatelet cytotoxicity assay was repeatedly negative, which indicates that platelet destruction in this patient was not mediated by antibody-induced complement activation. This is compatible with a recent report indicating that IgG-mediated erythrocyte autoimmunity involves removal by the reticuloendothelial system through F_c component recognition, while IgM-mediated antibodies tend to predominantly activate complement (20). Lizak and Grumet, however, were able to detect HLA antibodies against platelets with their procedure although we were unable to do so in our case. We feel that the distribution of the IgG antibody on the surface of the platelet may not have been dense enough to activate complement deposition. Removal of these IgG-coated platelets would then occur through F_c recognition by specific receptors in the reticuloendothelial system without the requirement for complement. This HLA antibody does not appear to be specific for virus-infected B lymphocytes, as it was detectable in tissue typing with cells of healthy adults. Unfortunately, the patient was not available for further testing using autologous cells after resolution of the leukopenia.

A number of "immunologic epiphenomena" occur with infectious mononucleosis including the production of anti-I, antinuclear antibodies, and rheumatoid factor. Consequently, anti-HLA antibodies may represent another as yet unrecognized immunologic reaction to this viral infection. Evidence for the clinical significance of these antibodies in the genesis of the varied manifestations of this disorder is not yet clear.

In summary, we have presented a case of infectious mononucleosis complicated by severe thrombocytopenia and neutropenia. The presence of a unique broad spectrum HLA antibody that decreased in titer over time lends support to its role in this disorder. This is the first description of a specific antigen

that may be involved in the pathogenesis of this autoimmune reaction.

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