Acute Epstein-Barr Virus Infection Complicated by Severe Thrombocytopenia

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We describe one patient with acute Epstein-Barr virus (EBV) infection associated with severe thrombocytopenia and review 36 additional cases reported in the literature. Complications of EBV infection due to severe thrombocytopenia occurred in 10 (27.0%) of 37 patients, and 2 (5.4%) of 37 patients died. Although acute EBV infections are generally benign and self-limiting, thrombocytopenia, a potentially serious complication, should not be overlooked.

Case Report

A previously healthy, 17-year-old Caucasian female presented to University of Tennessee Medical Center at Knoxville (Knoxville, TN) with a 2-week history of dizziness, lethargy, and fever and a 1-day history of lower-extremity petechiae. One week before hospitalization, she presented to her primary care physician with fever as well as anterior and posterior cervical adenopathy. History included the patient’s report that a friend had had “mono” earlier that month. The results of a peripheral blood count revealed a WBC count of 4,000/mm³ and a platelet count of 138 × 10³/mm³. The result of a Monospot test performed at that time was negative, and the patient started receiving therapy with clarithromycin.

Physical examination on admission to the hospital revealed a temperature of 38.3°C, right tonsillar swelling and erythema, soft-palate petechiae, and diffuse lower-extremity petechiae. Results of her initial laboratory examination were as follows: hemoglobin, 12.8 g/dL; hematocrit, 37.7%; peripheral WBC count, 8,200/mm³; and platelet count, 4 × 10³/mm³. A peripheral blood smear demonstrated severe thrombocytopenia, lymphocytosis with reactive features, and neutropenia (figure 1). Laboratory studies repeated several hours after admission revealed that the platelet count had decreased to 2 × 10³/mm³.

A bone marrow biopsy specimen and bone marrow aspirate were obtained. The patient was treated with parenteral corticosteroids, intravenous immunoglobulin (after blood for serological testing was obtained), and platelet transfusions. She did not experience bleeding or other complications.

A second Monospot test was performed for which the result was positive. EBV-specific serology was conclusive for recent infection. The titer of IgM antibody to viral capsid antigen was elevated (1:40, normal range <1:10; EBV-VCA-IgM ELISA [Clark Laboratories, Jamestown, NY]); the titer of antibody to early antigen-diffuse was elevated (1:20, normal range <1:10 [Gran Bio, Temecula, CA]), whereas the titer of antibody to early antigen-restricted was within the normal range (<1:10 [Gran Bio]); the titer of antibody to nuclear antigen was 1:2 (normal range <1:2 [Gran Bio]); and the titer of IgG antibody to viral capsid antigen was elevated (1:640, normal range <1:40 [Gran Bio]). Serological tests for evidence of ehrlichiosis, leptospirosis, Rocky Mountain spotted fever, cytomegalovirus (CMV) infection, and hepatitis B and hepatitis C were negative; a urine culture was negative for CMV, and an antinuclear antibody screen was negative as well. The patient was discharged to her home after 4 days with a platelet count of 51.0 × 10³/mm³; she was to continue corticosteroids to be taken orally on a tapering dose. Currently, ~2 months after onset of illness, she is well with a normal platelet count.

Methods and Results

A direct immunofluorescence assay was used to detect circulating platelet antibodies [2]. Both IgM (4+) and IgG (3+) platelet antibodies were evident in blood obtained from our patient. Examination of bone marrow core biopsy and aspirate demonstrated tri-lineage hematopoiesis without maturational abnormalities (figure 2). Megakaryocytes were identified in slightly increased numbers, and a mild lymphocytosis with reactive changes was also observed. The bone marrow biopsy specimen was analyzed for the presence of the nonpolyadenylated EBV RNAs (EBERs); these RNAs are transcribed abundantly in cells that are latently infected [3]. EBV-positive Raji cells bound anti-sense riboprobe, denoting presence of virus. EBV-negative control cells and the test sample of bone marrow

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Platelet antibody assays were done in 17 cases (46%); antibodies were detected in seven cases. The gender distribution of patients with demonstrable platelet antibodies was similar; four (40%) of 10 males and three (42.9%) of seven females had platelet antibodies.

Discussion

The etiology of severe thrombocytopenia in the setting of acute EBV infection is thought to be immune mediated [1]. Platelet antibodies were demonstrated in seven of the cases included in our review. Twenty-one of the 37 patients were not screened for antiplatelet antibodies; therefore, based on this review, it is not possible to determine the prevalence of these antibodies in patients who develop thrombocytopenia.

Splenic sequestration is another possible mechanism involved in the production of thrombocytopenia [1, 5]. Splenomegaly is often demonstrated on physical examination or by radiographic or ultrasonographic procedures in patients with acute EBV infection. However, the presence of splenomegaly in and of itself is not an indicator for the development of thrombocytopenia; patients with splenomegaly can have normal platelet counts, and patients with profound thrombocytopenia can have normal-sized spleens.

To our knowledge, in situ hybridization to determine the presence of EBV in the bone marrow of patients with associated severe thrombocytopenia has not been reported previously. It is tempting to speculate, because of the absence of discernible EBV in the bone marrow biopsy obtained from our patient, that a bone marrow functional abnormality was not the primary cause of severe thrombocytopenia and that peripheral consumption was prominent in the pathogenesis of this complication.

Successful treatment of EBV-associated thrombocytopenia can be difficult. Corticosteroids are most often used, but im-
provement in response to treatment can take 2–6 weeks, and treatment sometimes fails, even after an initial improvement in the patient’s condition [5]. On the basis of the findings in this review, it is difficult to predict, whether corticosteroids are of benefit, given that the large majority (78.1%) of patients received these agents. Platelet transfusions can be used but are often of only temporary benefit. Nevertheless, of those patients who received platelet transfusions, two times as many did not develop complications of severe thrombocytopenia. One or more doses of intravenous immunoglobulin have been used in some cases and resulted in increased platelet counts. Spontaneous resolution of thrombocytopenia may require 3 months or more.

Although severe EBV-associated thrombocytopenia is rare, it can have life-threatening consequences. This complication should be considered in any patient with acute EBV infection and evidence of mucosal or dermal bleeding, and patients should be advised to seek medical attention if signs of bleeding occur.

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