

CASE REPORT

Severe thrombocytopenia in an adolescent caused by Epstein Barr Virus

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Introduction

Infectious mononucleosis is an acute disease caused by the Epstein-Barr virus (EBV) and characterized by sore throat, fever, lymphadenopathy, splenomegaly and atypical lymphocytosis. It typically has a benign course and lasts approximately 3 weeks, but fatigue can persist for months. Serious complications, including death, have been reported but are rare.^{1,2} Accounts of a bleeding diathesis associated with this disease have long been observed.³ Hematologic complications of EBV include neutropenia in 50-80% of cases and hemolytic anemia in approximately 3% of cases.¹ Mild thrombocytopenia occurs in 25-50% of cases, but severe thrombocytopenia with platelet counts less than $20 \times 10^9/L$ is rare.¹ An earlier publication that reviewed cases between 1965 and 1997 identified 37 patients with this complication.² Our own MEDLINE search of “acute Epstein-Barr infection and severe thrombocytopenia” from 1998 until 2018 identified an additional seven cases.⁴⁻⁸ We herein report a case of an adolescent who presented with platelet levels of $3 \times 10^9/L$ in the setting of an acute EBV infection. Given that there are few reports of this rare complication in the literature, and the vast majority of reports were published over a decade ago, it would be prudent to educate current physicians on the possibility of an exceedingly low platelet count with this common viral illness and furthermore highlight the need to assess for an EBV syndrome in patients presenting with severe thrombocytopenia.

History

A 19-year-old Caucasian male student presented to the Halifax Infirmary Emergency Department with an approximate one-week history of fever, chills, sweats, nausea, abdominal pain, headache and nasal congestion. He had also lost about 10 lbs in the preceding 2-3 weeks when his appetite began to decline. His past medical history was significant for gastroesophageal reflux disease and for this he took pantoprazole 40mg orally once daily. His only other medication was ibuprofen as needed prior to playing hockey.

Examination

On presentation, his vital signs were within normal limits with a temperature of 37.6°C. He had wet purpura in his mouth and petechiae present on the

thorax and dorsal aspects of his feet and arms. He had tender head and neck adenopathy and inflamed tonsils. His abdominal exam revealed splenomegaly. Cardiac and respiratory examinations were unremarkable.

His initial complete blood cell count showed a haemoglobin of 141g/L, WBC $15.85 \times 10^9/L$ and platelets of $3 \times 10^9/L$. Platelet levels from previous bloodwork were within normal limits. Blood smear revealed severe thrombocytopenia with >70% atypical lymphocytes. Peripheral blood flow cytometry later showed reactive lymphocytes without a clonal population. INR was 1.1 and PTT 33 seconds. Liver testing showed a hepatitis with ALT 439 U/L, AST 267 U/L, ALP 299 U/L, GGT 181 U/L, with normal total bilirubin at 5.2 U/L. Hepatitis B surface antigen was negative and surface antibody was positive. Hepatitis C antibody, hepatitis A IgM, and HIV were negative. CMV IgG was positive. Blood cultures were negative. Anti-EBV nuclear antigen (EBNA) antibodies were negative and viral capsid antigen (VCA) IgM antibody was positive. To illustrate the meaning of these results, note that with the measurement of VCA IgG, VCA IgM, and EBNA IgG, one can distinguish acute from past infection; the presence of VCA IgM and VCA IgG without EBNA IgG indicates acute infection, whereas VCA IgG and EBNA IgG without VCA IgM suggests a past infection. Based on our patient's clinical syndrome and his positive VCA IgM, he was diagnosed with acute EBV and severe EBV-related thrombocytopenia.

Treatment/Course in Hospital

The patient was admitted to the Medical Teaching Unit and was cared for by the General Internal Medicine team with Hematology in consultation. He experienced one episode of epistaxis (relieved with pressure), as well as one episode of minimal hematochezia and hematemesis. His hemoglobin dropped from 141 to 126g/L, thus never necessitating a blood transfusion. His symptoms improved overall during his five-day admission. With regards to treatment, please see Figure 1 for a timeline and corresponding platelet levels. He was transfused with platelets to a threshold of $10 \times 10^9/L$. On days 2 and 3 of his admission, he was treated with intravenous immunoglobulin (IVIg, Figure 1). On day 4, he was started on a 5 day course of prednisone at 50mg/day and was discharged home on day 5 with platelets at $32 \times 10^9/L$. Approximately one week after

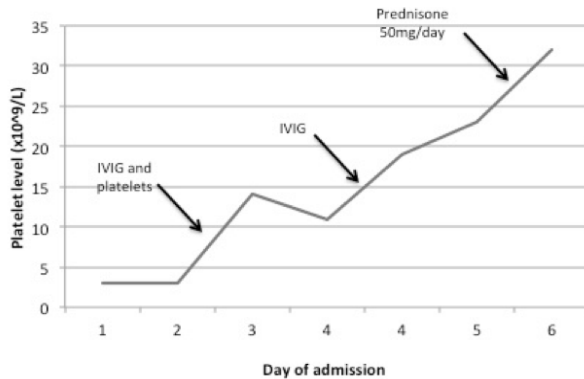


Figure 1: Timeline of treatment and platelet response in the inpatient setting for our case of severe thrombocytopenia in the setting of acute EBV infection.

completing his prednisone course, he presented to the Emergency Department a second time with ongoing thrombocytopenia (platelets $32 \times 10^9/L$) and persistent symptoms of mononucleosis (fatigue, malaise and dyspnea). He was given a longer course of prednisone, starting at 1mg/kg and tapered over a period of approximately 2 months, and his platelets recovered to normal values by the end of his prednisone course.

Discussion

Mild thrombocytopenia from acute EBV infection can occur in up to 50% of adult patients. From the literature, it would appear that individuals who develop severe thrombocytopenia secondary to acute EBV infection tend to be less than 21 years of age, and in such individuals platelet count nadirs below $10 \times 10^{10}/L$ can occur more frequently than one might expect.² Of the 37 cases identified by Pipp et al with platelet counts below $20 \times 10^{10}/L$, 75.7% were 21 years of age or younger and 78.4% of the 37 cases developed platelet counts below $10 \times 10^{10}/L$.² Of the patients that developed serious complications, 80% had counts below $10 \times 10^{10}/L$. Our patient was 19 and had severely low platelets but did not suffer any serious sequelae.

While severe thrombocytopenia complicating infectious mononucleosis may resolve spontaneously within days to weeks, treatment may be required.⁹ The mainstay of treatment, which is corticosteroids, often follows the guidelines for managing primary immune thrombocytopenia purpura as specific guidelines for viral induced thrombocytopenia are poorly defined.¹⁰ However, response to corticosteroids may take weeks.² Platelet transfusions can be used supportively but the effect is only temporary. IVIG should be used in the case of presence of extensive purpura or internal bleeding.^{10,11} IVIG can also be considered without extensive purpura or bleeding in the context of a platelet response below $5 \times 10^{10}/L$ that has not responded to corticosteroid therapy.^{10,11} The presence of extensive purpura in our

patient justified the use of IVIG as a first line therapy. The two doses of IVIG helped his platelets recover to near $20 \times 10^{10}/L$. Methylprednisone pulse therapy and high dose dexamethasone have also been used in cases where an urgent increase in platelets was necessary or platelet levels were refractory to corticosteroids.^{12,13} Refractory cases despite glucocorticoid/IVIG therapy with ongoing bleeding complications are considered for splenectomy, rituximab or thrombopoietin receptor antagonism. Importantly, it is necessary to avoid any drug that interferes with platelet function, such as aspirin and nonsteroidal anti-inflammatory agents. The majority of cases with thrombocytopenia recover from this acute complication. The development of chronic thrombocytopenia is possible but rare.

Various mechanisms have been proposed to explain thrombocytopenia with acute EBV infection. Autoimmune responses to the virus can generate antibodies against platelet membrane glycoproteins in about 40% of patients.² Splenic sequestration secondary to hypersplenism has also been proposed as an additional mechanism, however patients with severe thrombocytopenia may have normal spleen sizes, and those with splenomegaly may have normal platelet counts.⁵ Lastly, it has been proposed that in cases of thrombocytopenia purpura secondary to EBV, antiplatelet factors may be contributing to very short isologous platelet survival.¹⁴

In conclusion, severe thrombocytopenia secondary to acute EBV infection occurs rarely, but can lead to serious complications, typically in young adults and children. Acute EBV infection should be considered as a potential cause in patients with undifferentiated thrombocytopenia and a compatible clinical syndrome, while ruling out lymphoproliferative disease. If severe thrombocytopenia is confirmed to be secondary to EBV, corticosteroids are the mainstay of treatment. In cases where immediate platelet recovery is necessary, IVIG, pulse steroid therapy and supportive platelet transfusions can be used.

Consent

Written consent to publish this case report was obtained from the patient. The consent was fully informed, voluntary, written, and is within the possession of Dr. D. Haase.

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