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Hematologic Complications of EBV Infection in Children

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Abstract

Epstein-Barr virus (EBV) is a γ-herpesvirus which infects >95% of the world population. Infectious Mononucleosis is the most clinical condition caused by EBV, characterized by fatigue, fever, pharyngitis, lymphadenopathy and hepato-splenomegaly. Primary infection in children is usually asymptomatic or produce an acute illness that is often not recognized as being due to EBV. It is already known that EBV infection is usually benign but may occasionally be associated with pathogenic consequences. We report the case of an 11 years male patient with thrombocytopenia combined neutropenia due to EBV infection.

Keywords: EBV; Thrombocytopenia; Neutropenia; Infection; Children

Introduction

Epstein-Barr virus (EBV) was discovered in 1964 by electron microscopy of suspension cultures of African Burkitt lymphoma cells [1]. Four years later, EBV was linked conclusively to infectious mononucleosis, which is its most common clinical manifestation [2]. EBV is one of the eight known human herpesviruses, and like other herpesviruses, results in lifelong infection after primary infection. Initial infection is thought to occur in the oral (tonsillar) compartment and the host cells of EBV are mainly lymphocytes and epithelial cells. Infected memory B cells are released into the peripheral circulation, their number decreases over time after the onset of symptoms of primary infection, but these cells are never eliminated entirely [3]. Children acquire primary EBV infection from close contact that involves exchange of oral secretions via shared items such as toys, bottles, and utensils. In early childhood, primary infection is usually asymptomatic or produces an acute illness that is often not recognized as being due to EBV . In adolescents and young adults, however, primary EBV infection frequently presents as infectious mononucleosis, which is characterized by fever, fatigue, pharyngitis, lymphadenitis and hepato-splenomegaly. Primary EBV infection occurs at a younger age among persons from lower versus higher socioeconomic backgrounds, which has been attributed to crowded living conditions [4]. Healthy people continue to shed EBV for many months after their acute infection and are potentially capable of transmitting it [5,6]. Infectious mononucleosis most often begins insidiously, with vague malaise, followed several days later by fever, sore throat, swollen posterior cervical lymph nodes, and fatigue. Some patients experience an abrupt influenza-like onset, with fever, chills, body aches, and sore throat [7-11]. The median duration of infectious mononucleosis is 16 days, which is much longer than the duration of most acute viral illnesses, recovery is gradual, and it may take months for the patient to feel entirely well [11]. Complications may be due to tissue-invasive viral disease or to immune-mediated damage.

Case Report

A 11-years old male, previously healthy, admitted to the University Hospital Center of Tirana with a history of 7-days high fever and fatigue. On physical examination he appeared ill. The pharynx was injected without exudates. Cervical lymph nodes were not palpable. The abdomen was soft, not tender or distended. Liver and spleen were both palpable 3-4cm under the costal margin. On the skin were observed petechiae on the back and over the elbows.

Laboratory investigations on admission revealed a blood cell count WBC 2700cells/mm^3, 32% were neutrophils (864 ANC mm^3), RBC 4,970,000cells/mm^3, hemoglobin level 12.1g/dl, hematocrit value 36.8%, platelet count PLT 11,000cells/mm^3.

Aspartate aminotransferase (AST) 40U/L (nr 0-35U/L), alanine aminotransferase (ALT) 35U/L (nr 0-45 U/L), prothrombin time/ international normalized ratio (INR) 1.14, blood urea nitrogen 30mg/dL (nr 10-43 mg/dL), creatinine level 0.5mg/dL (nr 0.6-1.4mg/dL), serum total protein level 6.8g/dL (nr 6-8g/dL).

As thrombocytopenia was combined with neutropenia , bone marrow aspirate examination was performed to exclude myelodysplastic syndrome. The cellularity of the aspirate and morphology of erythroid and myeloid precursors were normal, the number of megakaryocytes was increased. Laboratory research for CMV, HIV, Parvo virus 19 were negative. The EBV panel results indicated acute primary infection: IgM antibodies against viral capsid antigen (VCA) were positive 62.49arbU/ml, (neg < 10arbU/ml), whereas VCA-IgG antibodies were negative 1.6arbU/ml (neg < 5arbU/ml).

The recovery was spontaneous with normal neutrophils and platelet counts in 1 week.

Discussion

It has been over 50 years by now that EBV was discovered and linked to Infectious Mononucleosis. It is also known for its human tumoral effects and is associated with several cancers including B-cell lymphomas (Hodgkin disease, Burkitt and immunoblastic lymphomas), carcinomas (nasopharyngeal and gastric) and also has been linked to several autoimmune diseases.

Thrombocytopenia is not an uncommon feature of EBV, it is found in up to one-third of cases in children. In general, it is transitory and mild and rarely pose the child in risk for hemorrhagic complication. In the presenting child the number of platelets was considerably low 11,000cells/mm^3 with concomitant hemorrhagic elements on the skin. Platelet numbers decrease due to platelet destruction and/or diminished platelet production. Potential pathogenic causes of this process are infections including EBV, CMV, hepatitis viruses and HIV, for this reason a full research was conducted to discover the etiologic cause of thrombocytopenia with EBV infection as the final result. In viral diseases including EBV , the mechanisms of thrombocytopenia are multi factorial, usually related to possible deterioration of the immune system that may be caused by antiplatelet antibodies or immune complexes, faulty platelet generation or an altered reticuloendothelial performance [12,13]. The autoimmune system course of action is assumed to occur within the spleen; however, no analysis has revealed EBV protein expression in the spleen [14].

Neutropenia is a decrease in circulating neutrophils in the non-marginal pool and is defined in terms of the absolute neutrophil count (ANC). The lower limit of the reference value for ANC is 1500cells/mm^3. Mild neutropenia is present when the ANC is 1000-1500cells/mm^3, moderate neutropenia is present with an ANC 500-1000cells/mm^3 which is the range in the presenting child. Severe neutropenia refers to an ANC lower than 500cells/mm^3 and is associated with greater risk of infections. Mature neutrophils are produced in the bone marrow and after entering the blood leave it in a random way after 6-8 hours, thereafter they enter in the tissues destined for cellular action or death. The mechanisms that cause neutropenia are not completely understood too, are due to the inadequate production in bone marrow or increased destruction in blood or tissues.

The ability of the bone marrow to produce blood cells required on a daily basis depends on a highly regulated process of proliferation and differentiation of hematopoietic stem (HSC) and progenitor cells (HSPC), which is rapidly adapted under stress conditions , such as infections to meet the specific cellular needs of the immune response and the physiological changes. Many acute viral infections including EBV induce transient alterations on the hematopoietic process, through the action of mediators such as type I INFs, TNF and lymphotoxin, but these effects are generally overlooked in many human acute viral infections because of their subclinical nature [15,16]. The mechanisms by which infections in general can influence the bone marrow biology are direct infection and through the pro-inflammatory cytokines released and changes in bone marrow micro-environment.

EBV infection may permanently alter or impair the immune response. A potent innate and adaptive immune response occurs during primary EBV infection. The innate immune system is an important first line defense against all viral infections which elicit a strong type I interferon (INF) response early after infection. High levels of INFα directly induce HSCs to exit quiescence and transiently proliferate, which is wired because most cell types stop proliferating in response to INFα [17,18]. Type I INF driven HSC proliferation is a transient event, this proliferation burst fails to exhaust the HSC pool. After the first wave of type I INF produced by infected cells, type II INF (INFγ), produced by stimulated T cells and NK cells, also contributes to the impairment of HSC self-renewal. INFγ triggering on HSPCs enhances monocyte formation, but this is on the expense of the production of neutrophilic and eosinophilic granulocytes , B cells and erythrocytes [19,20]. INFγ is the most prominent cytokine produced in acute Infectious Mononucleosis and is important in controlling EBV infection and reactivation. High levels of INFγ contribute to the symptoms experienced during Infectious Mononucleosis, as the cytokine is known to cause headache, fatigue and fever.

Conclusion

Hematologic complications are well known in primary EBV infection. Thrombocytopenia, which is usually mild, transitory and of autoimmune origin, but sometimes may be profound and prone to acute hemorrhagic complications. Leukopenia and neutropenia are a rare finding, caused by the direct acute viral infection, and are transitory too. When thrombocytopenia and neutropenia co-exist, a bone marrow examination is required to exclude any potential myelodysplastic syndrome.

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