Case Report

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Infectious Mononucleosis Mimicking Acute Lymphoblastic Leukemia (ALL): A Case Report

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ABSTRACT

Infectious mononucleosis (IM), usually caused by Epstein-Barr virus (EBV), is not rare among populations. Fever, pharyngotonsilitis and lymphadenopathy are its major presentations. Since EBV mainly targets lymphomononuclear cells and the reticuloendothelial system, it might be mistaken with hematological malignancies. The case presented in this article showed a very high similarity to an acute lymphoblastic leukemia, which complicated the diagnostic work-up. The histopathological data and clinical course of IM patients are not usually distinctive; hence, early work-up for EBV-associated IM is suggested.

Introduction

Epstein-Bar Virus (EBV), also known as human herpesvirus 4, is a common pathogen that affects 90% of the adult population and spreads by oral contact or saliva. Both innate and adaptive immune responses are actived during the infection with EBV, but the virus will not be cleared completely. The EBV virus can induce a latent infection in B-lymphocytes [1], which will subsequently cause exaggerate proliferation in CD8 positive T cells, however, during the acute stage of infectious mononucleosis, the population of memory CD8+ cells will decrease [2].

Most EBV infections are not noticeable. The systemic manifestations of EBV infection are recognized as the differential diagnosis of systemic disorders such as lymphoproliferative disorders (LPD). There are different types of LPDs caused by EBV infection, based on the exact type of cells which are affected [3]. Primary infection usually has no symptoms, but infectious mononucleosis (IM) can be seen in children and more frequently in adolescents. The incidence of EBV-associated infectious mononucleosis is about 1.6–99 cases per 100,000 individuals; however, in industrialized countries, the risk of IM will increase [4].

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IM, also known as glandular fever, is characterized by cough, fever, cervical lymph node enlargement, fatigue and sore throat. It is usually a self-limiting disease which is generally caused by EBV. A minority of cases present infection with human cytomegalovirus (CMV) and other infectious agents 5. Several complications such as certain cancers and various autoimmune disorders can be accompanied with IM [5].

The triad of fever, pharyngitis and lymphadenopathy will appear in IM patients, but the diagnosis is based on detection of atypical lymphocytes (large, irregular nuclei) greater than 15% in the peripheral blood cells [6]. Atypical lymphocytes, which are indicators of viral or non-viral infections, should not be misdiagnosed with abnormal lymphocytes manifesting in lymphoreticular malignancies (e.g., leukemia and lymphoma). Atypical lymphocytes have been discovered in a variety of clinical disorders such as IM, collagen diseases and other autoimmune conditions, and blood malignancies7. We, herein, discuss a case of EBV-related IM, which completely mimicked the observations and symptoms of acute lymphoblastic leukemia (ALL).

Case Presentation

A 22-year-old woman presented to the emergency department with sore throat and fever. The physical examination revealed generalized maculopapular rash, occipital and behind the ears lymphadenopathy (LAP), frontal headache and facial edema, which appeared after administration of antibiotics in another medical facility (8 capsules of co-amoxiclav and 10 capsules of amoxicillin). Her WBC count was 18.8 × 10^9/L, as well as a Hb level of 12.2 g/dl and platelet count of 249 × 10^9/L at first impression.

Blood biochemistry showed elevated levels of alkaline phosphatase (ALP) of 314 IU/L, lactate dehydrogenase (LDH) of 2916 IU/L, and an erythrocyte sedimentation rate (ESR) of 8 mm/hr. Blood sugar was in normal range (61-71). The patient had a normal total bilirubin level and urine analysis was normal.

During hospitalization, the platelet count decreased progressively (249000, 209000, 125000, 105000, 69000, 43000, 31000, 26000), the WBC count increased and leukocytosis progressed (18790, 25200, 22730, 19300, 26920, 51090, 73540) and LDH level was constantly higher than normal (2916, 1803, 1580, 1917, 2555, 2350, 1679, 1400, 1122).

Pathological examination detected atypical lymphocytes in peripheral blood cells (PBC). Presence of hepatosplenomegaly was seen in diagnostic ultrasonography; hence hematological disorders such as malignancies were suggested. Bone marrow aspiration was conducted, which found multifocal granulomatosis inflammation along with lymphocytosis. The acid-fast stain for tubercle bacilli was negative.

Histopathological work-up showed a T cell population (about 85% of the lymphocytic gate with low CD4/CD8 ratio: 1/6). The B cells were markedly decreased and the analysis of cells in the monocytic area showed monocytic components to the extent of 33% of all analyzed cells. These findings showed a significant increase in monocytic components and CD8 positive T cells. The megaloblastic changes were detected in erythroid maturation. Normochromic, normocytic cells and many burr cells were seen in RBC morphology.

The patient was referred to the hematology ward due to the primary diagnosis of acute lymphoblastic leukemia. Because of the progressively decreasing trend of platelet count, Prednisolone (1mg/kg) was administered as the initial treatment. After two weeks, the patient's general condition improved, and Hb level and platelet count were corrected after corticosteroid treatment.

Immunology tests showed negative results for anti-dsDNA and C-ANCA but positive P-ANCA. Due to these results, the possibility of systemic lupus erythematosus was excluded. The ELISA tests for HbsAg, HIV and HCV Ab were also negative.

The secondary analysis of PBCs detected lots of pre-lymphoblastic cells, and thus the diagnosis of ALL was ruled out. The bone marrow pathology specimens revealed fragments of tissue, including bone and intertrabecular marrow spaces. The cell to fat ratio was in order of 75 to 25. The majority of hematopoietic cells were substituted by monocytoid lymphocytes. The granulocytic series showed a shift to the left with segmented neutropenia. The erythroid elements were also decreased. PBC represented lymphocytosis with atypical monocytes, lymphocytes (Downey cells), and monocytosis. IHC stains for TDT, c-kit, CD10 and CD34 were negative in lymphoid cells.

The patient was discharged with IM diagnosis and underwent follow-up for 3 months after discharge from the hospital. The WBC and platelet count became normal and lymphadenopathy disappeared progressively. Ultrasonography results presented improvement of hepatosplenomegaly.

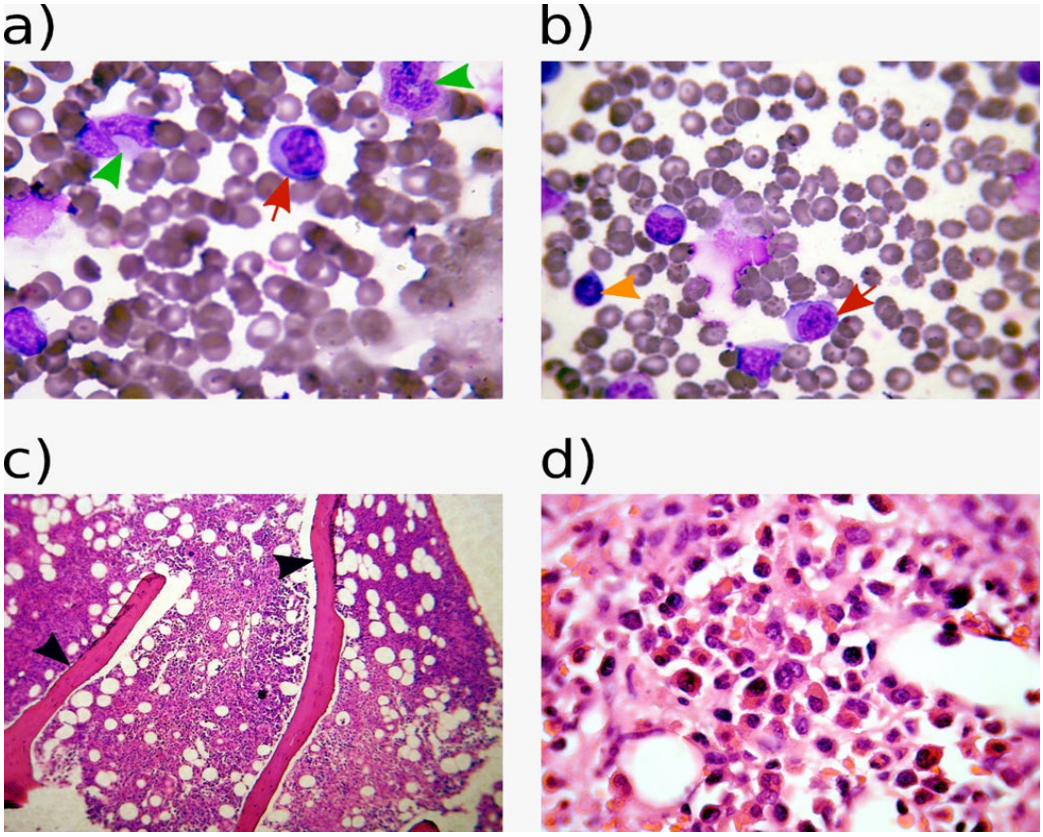

Fig. 1. *a) peripheral blood smear representing band cells (green arrows) and Downey cell (red arrow). b) peripheral blood smear representing normal lymphocytes (orange arrow) and Downey cell (red arrow). c) Bone trabeculae and marrow spaces with about 80% cellularity are present including trilineage population of hematopoietic cells (black arrow). d) Bone marrow aspiration smear showing no apparent malignancy.*

Discussion

The most prevalent cause of infectious mononucleosis (IM) is infection with EBV. There is a wide range of symptoms, from low sensitive criteria such as fever, hepatosplenomegaly, and jaundice to rare conditions such as autoimmune hemolytic anemia [8]. The pathogenesis of IM can be described as a primary infection of B lymphocytes and a vigorous proliferation of cytotoxic T cells. The T cell immune response leads to an increasing number of atypical lymphocytes (Downey cells) which consist of CD8+ T cells and CD16+ natural killer cells in peripheral blood [9].

ALL usually manifests as a multi-organ disease due to the direct infiltration of leukemic cells in various organs or by reduced production of normal marrow elements [10]. Previous studies have described cases of IM preceding ALL. The distinct association between EBV, IM and ALL is far from obvious. There is evidence that a common viral etiology exists for both IM and ALL, confirmed by serological findings [11, 12]. A study by Callan *et al*. showed that the majority of EBV-associated T lymphoblasts present activated/memory phenotype with up-regulation of CD38, CD45RO and HLA-DR, decreased expression level of CD62 leukocyte (CD62L), and down-regulation of CD45RA [13]. In such cases, the B cell population is decreased inconsistent with a marked increase in CD8+ T cells. As a result, the ratio of CD4+/CD8+ was 1/6, which reflects massive CD8+ generation.

Lymphoproliferative disorders (LPDs), especially ALL, can completely masquerade as EBV-associated IM due to a T cell proliferation following B cell reduction [14]. One of the best solutions to this challenge might be diagnosis of EBV-related IM based on the PCR method to detect the viral genome and viral serology markers (e.g., VCA IgG, VCA IgM and EBV nuclear antigen EBNA-1 IgG) [15].

Although previously there were reports about unusual presentations of EBV that led to either a delayed onset or delayed diagnosis of a malignancy such as CHL [16], no older report was found to consider the opposite in connection with ALL. The alertness of the clinicians regarding the possibility of IM mimicking ALL might prevent further invasive diagnostic procedures [17], considering the fact that the majority of the patients with IM can recover with supportive care. The case presented in this article reminds us of the various faces of EBV infection. Hence, it is paramount to note that, during differential diagnosis of LPDs, infectious agents that may cause similar symptoms are not be neglected.

Ethical Considerations

Compliance with ethical guidelines

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent for publication has been obtained from the patient to publish this report and its figures in accordance with the journal's patient consent policy.

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Conflict of interest

The authors declared no conflict of interest.

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