A rare case of three distinct Epstein-Barr virus associated lymphoproliferative disorders over sixteen years of human immunodeficiency virus infection

Hamdy M.A. Ahmed,[1] Abrar Khan,[1] Weyman Lam,[1] Samar Abohamad,[2] Pradyumna Phatak[3]

[1]Department of Internal Medicine, Rochester General Hospital, Rochester, NY, USA; [2]Department of Internal Medicine, Cairo University Hospitals, Cairo, Egypt; [3]Division of Hematology and Oncology, Department of Internal Medicine, Rochester General Hospital, Rochester, NY, USA

Abstract

Epstein Barr virus (EBV) is well known to cause different types of malignancies. In immunocompromised patients, such as those infected with human immunodeficiency virus (HIV), there is a higher likelihood of EBV related malignant transformation. Diagnosis of EBV related malignancies may be difficult and sometimes requires clinical and pathological correlation. It is very rare to have more than one type of EBV related malignancy in a single patient. Until now, there are no specific guidelines for treatment of EBV related malignancies and lymphoproliferative disorders (LPD). We present a patient who developed three different types of EBV related LPD during a sixteen-year course of HIV infection.

Introduction

Infection with Epstein Barr virus (EBV), or human herpesvirus-4, is ubiquitous worldwide in human populations and is associated with several diseases whose incidence differs dramatically in different parts of the world.[1] EBV can cause a wide spectrum of diseases, including infectious diseases and malignancies, most commonly of lymphoid origin. In fact, it was the first virus known to directly cause a malignant disorder.[2] Human Immunodeficiency virus (HIV) is an infectious cause for acquired immunodeficiency and is associated with increased relative risk of lymphoma incidence. With the introduction of highly active antiretroviral therapy (HAART), there was a dramatic decrease in incidence of lymphomas in HIV patients.[3] Lymphoproliferative disorders in HIV patients are more likely to be associated with EBV than those in individuals with no immune compromise.

Case Report

We present a 60-year-old African American male with known HIV infection since 2000. He was variably compliant with prescribed anti-retroviral therapy. During a hospital admission for severe pneumonia in 2004, he was found to have an elevated LDH and abdominal lymphadenopathy. His bone marrow biopsy showed infiltration with immature lymphoid cells with vacuoles morphologically compatible with high grade Burkitt's lymphoma that were positive for CD 20, CD 10, and CD 79a by immunohistochemical studies. He had systemic treatment with hyper-CVAD regimen (Cyclophosphamide, Vincristine, Adriamycin and Dexamethasone) and intrathecal methotrexate alternating with systemic high dose methotrexate and cytosine arabinoside. Complete remission was achieved and he remained stable on antiretroviral therapy till 2007 when he presented to the hospital with new onset flank and back pain. Imaging studies revealed diffuse adenopathy, and excisional iliac lymph node biopsy was diagnostic of Hodgkin lymphoma, subtype mixed cellularity. Hodgkin cells were diffusely positive for EBV latent membrane protein 1 (LMP-1) and EBV encoded RNA (EBER) by in situ hybridization. He was treated with dose-reduced ABVD regimen (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) due to poor bone marrow tolerance, and achieved a complete clinical remission. He was maintained on TRIPLA with HIV viral load ranging from 0-70 copies/mL and CD4 count >400/mm^3. In 2015, he developed shortness of breath and a cough with scanty sputum and required admission to the hospital for worsening hypoxia. Microbiologic workup was negative for infectious etiologies. A chest CT scan showed extensive diffuse irregular nodular and airspace opacities mainly affecting the right middle lobe and both lower lobes with peri-lymphatic distribution, along with mildly enlarged hilar lymph nodes (Figure 1). Trans-bronchial fine needle aspiration of the hilar lymph nodes showed reactive lymph nodes with no signs of malignancy. Flow cytometry did not show abnormal proliferation, and bronchoalveolar lavage was not conclusive for malignancy or an infectious etiology. Surgical wedge biopsy with the pleura showed cryptogenic organizing pneumonia with no evidence of infection or malignancy. The patient was started on steroids, which resulted in initial improvement, and was discharged to home on room air. Over the following weeks, he developed worsening hypoxia that was not responsive to treatment. Immunoassays and in situ hybridization for EBV of the lung biopsy showed polymorphic EBV-associated B-cell lymphoproliferative disorder (Figures 2 and 3). He was started on weekly Rituximab for four weeks after which his oxygen requirements were stabilized. Rituximab was continued for monthly treatments, and Bortezomib was added with no additional benefit. He is currently on Rituximab maintenance therapy every two months.

Correspondence: Hamdy Mohamed Abdelaziz Ahmed, 39 Rochester General Hospital, Rochester, NY, 14621 USA.
E-mail: hamdy.ahmed@rochesterregional.org, dr.hamdy86@gmail.com

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Discussion

EBV is transmitted through oral contact and saliva. It replicates in the pharyngeal mucosa before entering circulating B lymphocytes where its genome is replicated resulting in transformation of B lymphocytes into lymphoblastoid cells that induce humoral and cellular immunity. However, a minor portion of those cells can go into latent phase and escape the immune system by stopping protein synthesis resulting in formation of memory cells.[1] Disruption of immune response to lymphoblastoid cells can result in clonal expansion and lymphoid malignancies. EBV can cause several types of malignancies, including nasopharyngeal carcinoma, nasal T/NK lymphoma, Burkitt lymphoma (BL), Hodgkin lymphoma (HL), diffuse large B cell lymphoma (DLBCL), post-transplant lymphomas and HIV related lymphomas. The latter can be classified into lymphomas that can occur in normal population as HL, BL, DLBCL and peripheral T cell lymphomas, and lymphomas that are exclusive to HIV and immunodeficiency states as primary effusion lymphoma (PEL), plasmablastic lymphoma (PBL) of oral cavity and polymorphic B-cell lymphoma.[2]

Incidence of HIV related lymphoma may be attributed to multiple risk factors such as immunosuppression, cytokine dysregulation, chronic antigen stimulation, and opportunistic infections with oncogenic viruses such as EBV and Human Herpes Virus 8.[4] Our patient had three distinct types of EBV-related lymphoproliferative disorders (LPD) during his sixteen years of HIV infection. It is reported that EBV can be found in up to 50-60% of HIV related lymphomas with nearly 100% of primary CNS lymphomas, 80% of DLBCL with immunoblastic features, 30% to 50% of BLs, 60% of PBLs of oral cavity, 70% of PELs, and nearly 100% of HLs arising in the setting of HIV infection. BL is estimated to account for about 50% of non-Hodgkin's lymphomas in HIV patients. Although some EBV proteins are found consistently in BL cells, the potential oncogenecity of these proteins is known to be weak and thus it is suggested that HIV oncogenic role is required in addition to EBV infection for BL to occur in those patients. This may be supported by the fact that BL is not as common in immunosuppressed patients as in HIV.[5] In contrast, HL is very common in HIV patients with an incidence of 11-18 times higher than normal population. HL in HIV patients is associated significantly with EBV more than HL in non-HIV patients and usually presents with advanced stage.[6]

A gold standard method for EBV detection in malignant tissues is the *in situ* hybridization for EBV-encoded RNA (EBER). The significance of serum testing for EBV in this setting is less clear. Recent studies have shown that measuring the EBV viral load was a useful tool to predict EBV-related LPD in post-transplantation patients.[7] However, results are not the same with EBV-related LPD in HIV patients; Fan *et al*. found that patients with EBV related lymphomas had higher EBV viral loads, using PCR techniques, when compared to non-EBV related lymphomas and opportunistic infections in HIV patients. Those high loads fell rapidly after initiation of lymphoma therapy in almost all the patients.[8] Detecting EBV DNA, using PCR techniques, of CSF in patients with HIV was highly associated with primary central nervous lymphoma and non-HL.[9] In other studies, results did not show the same relationship.[10] Our patient was variably compli-

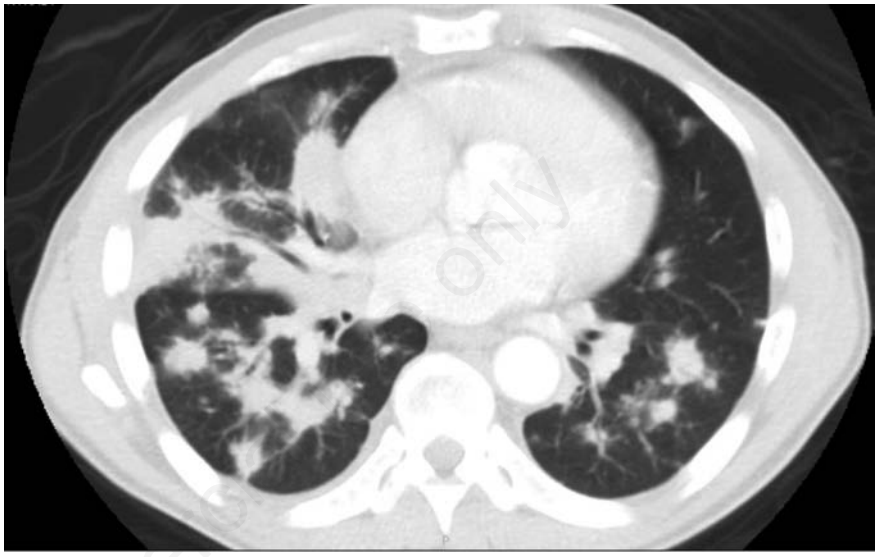

Figure 1. Computed tomography of the chest showing extensive diffuse irregular nodular and airspace opacities mainly affecting the right middle lobe.

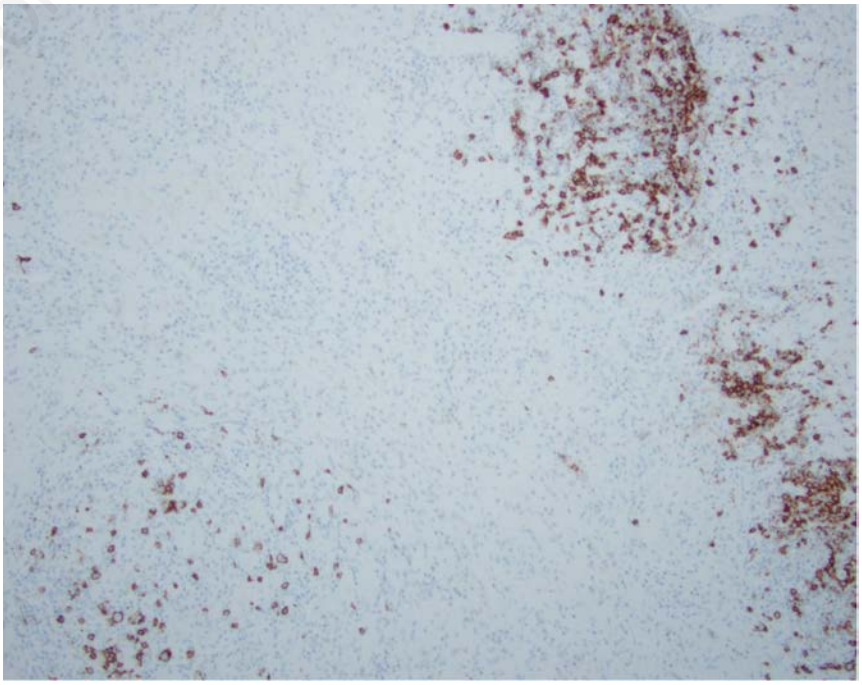

Figure 2. Positive CD20 stain.

ant with antiretroviral therapy when the first lymphoma occurred. His second lymphoma (HL) occurred in the setting of low HIV load and higher CD4 counts which suggested better compliance. His HIV infection was still well controlled when the third lymphoproliferative disorder occurred. This is consistent with the finding by Fan *et al.* that there was no relation between either the viral loads or the CD4 count and the occurrence of lymphoproliferative disorder in HIV patients.[8]

There are several suggested therapeutic approaches for EBV induced LPD, but no established guidelines. Antiviral therapy has not shown promising results and this may be due to the fact that it requires the virus to be in the lytic stage to be effective. One of the new approaches includes induction of the lytic phase of the virus, as by chemotherapy, followed by treatment with antivirals but it is still not well studied. The use of monoclonal antibodies, such as anti CD-20, has shown promising results. However, some drawbacks include limited B-cell depletion to 6-8 months and inability of stimulation the cellular immunity against EBV, which is required for long-term control. Bortezomib, which targets oncogenic pathways, has been found to induce apoptosis in EBV lymphoblastoid cells. Adoptive immunotherapy using EBV-specific cytotoxic T-lymphocytes, which is the same strategy used for treatment of cytomegalovirus in transplant patients, is still being under research. However, costs, graft versus host disease and tumor resistance are among the disadvantages of this strategy.[2,11] In HIV patients, there are few case reports of tumors regression with the use of HAART alone.[12-15] Our patient was already on HAART when he developed the second and third lymphoproliferative disorders. He was treated with anti-CD 20, Rituximab, which helped to slow the progression of the disease. Bortezomib was not effective. He is currently on Rituximab alone. Cyto-reductive options may be limited by his poor marrow tolerance.

An extensive literature review revealed multiple cases of single lymphoproliferative disorders in HIV patients. We only found two case reports with more than one type of EBV related lymphoproliferative disorders described in a patient with HIV. In 1990, Guarner described a 44 year-old male with HIV who was diagnosed with simultaneous HL of mixed cellularity and DLBCL in which in situ hybridization showed EBV DNA.[16] In 1991, Montalban reported a 22-year-old male with HIV who was diagnosed with HL. The patient achieved remission with chemotherapy but after three years he was diagnosed with DLBCL in which the EBV genome was found. He received chemotherapy but died within weeks from sepsis.[17]. Another report by Ambrosio *et al.* in 2015 described an HIV patient with simultaneous EBV-related LPD in the stomach along with nodal DLBCL, but couldn't prove that EBV caused his DLBCL.[18] We found two case reports of multiple EBV related LPD in patients without HIV. In 1996, Kingma *et al.* reported a 4-year-old girl who had cardiac transplantation at age of 23 months. Sixteen months later, she developed large cell lymphoma that was treated with IVIG and interferon. Eight months later, she had recurrence that was treated with chemotherapy. Later, she developed liver nodules that were diagnosed as smooth muscle tumor. The large cell lymphomas and the smooth muscle tumor contained EBV >95% by *in situ* hybridization.[19] In 2009, Murase *et al.* reported a 71-year-old male who developed lymphadenopathy, fever and weight loss. He was diagnosed with mixed cellularity HL. One year later, he developed lymphadenopathy and was diagnosed with DLBCL. Two years later, he had recurrence of HL. Both lymphomas were positive for CD20 and EBER.[20]

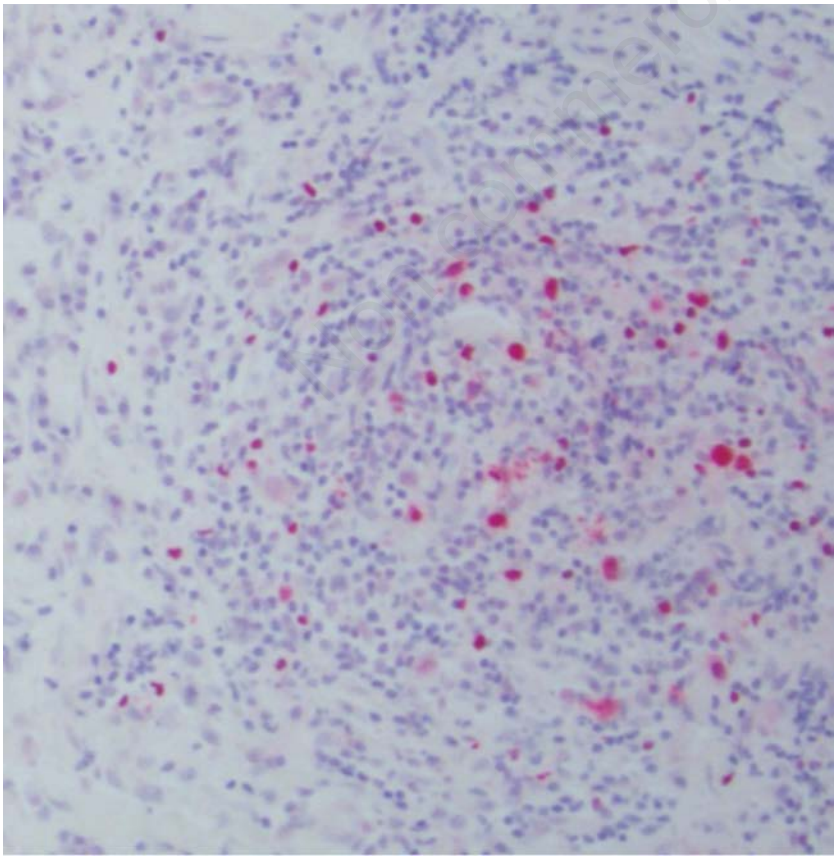

Figure 3. Positive *in situ* hybridization for Epstein-Barr virus encoded RNA.

Conclusions

In conclusion, we believe this is the first report of a patient with three distinct non-simultaneous EBV-related lymphoproliferative disorders in presence of HIV. EBV should be suspected in patients with different types of lymphoproliferative disorders occurring at the same time or at different times. So far eradication of the virus remains a challenge and there is no much evidence that this would prevent further lymphoproliferative transformation.

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