



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>

# Case Report

## EBV-Positive Diffuse Large B-Cell Lymphoma in Young Immunocompetent Individuals

Brady E. Beltran,<sup>1</sup> Domingo Morales,<sup>2</sup> Pilar Quiñones,<sup>2</sup> L. Jeffrey Medeiros,<sup>3</sup>  
Roberto N. Miranda,<sup>3</sup> Jorge J. Castillo<sup>4</sup>

### Clinical Practice Points

- Epstein-Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL) of the elderly is a novel entity defined by age > 50 years, lack of underlying immunodeficiency, and lymphoma composed of sheets of large B-cells, which has been associated with an aggressive clinical course and a poor prognosis.
- We present clinicopathological data on three immunocompetent individuals who were younger than 50 years of age but would otherwise meet criteria for EBV-positive DLBCL of the elderly.
- EBV-positive DLBCL of the elderly can occur in young immunocompetent patients, and we suggest that the age criterion, and possibly the name itself, be modified.

*Clinical Lymphoma, Myeloma & Leukemia*, Vol. 11, No. 6, 512-6 © 2011 Elsevier Inc. All rights reserved.

**Keywords:** Diffuse large B-cell lymphoma, EBV, Immunocompetent, Young

### Introduction

The 2008 World Health Organization (WHO) classification of lymphoid neoplasms uses morphological, immunophenotypic, genetic, and clinical criteria to define more than 30 types of B-cell leukemia and lymphoma.<sup>1</sup> The most common lymphoid neoplasm worldwide is diffuse large B-cell lymphoma (DLBCL), which accounts for approximately 30% of all lymphomas (including B- and T/NK-cell neoplasms).<sup>2</sup> The category of DLBCL is heterogeneous and encompasses a variety of clinicopathologic, immunophenotypic, and molecular features. The clinical course of patients who have DLBCL can be difficult to predict, which led to a search for clinical and/or pathological factors that can be used to risk-stratify these patients, including the International Prognostic Index (IPI) score,<sup>3</sup> immunophenotype,<sup>4</sup> and a variety of high-throughput methods including gene expression,<sup>5</sup> array comparative genomic hybridization,<sup>6</sup> and microRNA profiling.<sup>7</sup>

Chronic infection by Epstein-Barr virus (EBV) has been etiologically associated with a wide variety of lymphoma types. A limited list of EBV-associated lymphomas includes Burkitt lymphoma,<sup>8</sup> plasmablastic lymphoma,<sup>9</sup> extranodal NK/T-cell lymphoma (nasal type),<sup>10</sup> angioimmunoblastic T-cell lymphoma,<sup>11</sup> and classical Hodgkin lymphomas.<sup>12</sup> In the 2008 WHO classification of lymphomas, a newly described entity, EBV-positive DLBCL of the elderly, has been included. This neoplasm occurs in apparently immunocompetent patients who are older than 50 years of age.<sup>13</sup> These neoplasms resemble other cases of DLBCL, not otherwise specified, except that evidence of EBV infection is present in a substantial number of the neoplastic cells.

This report describes three patients, 25 to 34 years of age, who had no evidence of underlying immunosuppression and a diagnosis of EBV-positive DLBCL. The occurrence of these cases suggests that EBV-positive DLBCL is an entity that is not restricted to patients who are older than 50 years of age, and that the age criterion and possibly the designation of this disease must be modified in the next version of the WHO classification.

### Patients and Methods

#### Case Selection

Between January 2002 and June 2010, newly diagnosed patients with a pathological diagnosis of DLBCL, not otherwise specified (WHO classification), were identified from the medical records of the Hospital Nacional Edgardo Rebagliati Martins in Lima, Peru. Each neoplasm was composed of sheets of large cells and met the criteria for DLBCL as described in the WHO classification upon

<sup>1</sup>Department of Oncology and Radiotherapy, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru

<sup>2</sup>Department of Pathology, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru

<sup>3</sup>Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX

<sup>4</sup>The Warren Alpert Medical School of Brown University, Division of Hematology and Oncology, The Miriam Hospital, Providence, RI

Submitted: May 27, 2011; Revised: Jul 8, 2011; Accepted: Jul 15, 2011

Address for correspondence: Jorge Castillo, MD, The Miriam Hospital, 164 Summit Ave, Fain Building, Providence, RI 02906

Tel: 401-793-4645; fax: 401-793-7132; e-mail contact: jcastillo@lifespan.org

**Table 1** Clinical Characteristics of Three Young Patients With EBV-Positive DLBCL

| Case | Age | Sex | Performance | LDH      | Stage | aalPI Score | Therapy  | Response | Survival (Mo) | Outcome |
|------|-----|-----|-------------|----------|-------|-------------|----------|----------|---------------|---------|
| 1    | 25  | M   | 0           | Elevated | 2A    | 1           | R-CHOP   | CR       | 13            | Dead    |
| 2    | 34  | M   | 2           | Elevated | 3B    | 3           | CHOP     | NE       | 3             | Dead    |
| 3    | 34  | F   | 2           | Elevated | 3B    | 3           | CVP/CHOP | CR       | 59            | Alive   |

Abbreviations: aalPI = age-adjusted International Prognostic Index; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CR = complete response; CVP = cyclophosphamide, vincristine, prednisone; DLBCL = diffuse large B-cell lymphoma; EBV = Epstein-Barr virus; LDH = lactate dehydrogenase; NE = not evaluable; R = Rituximab.

**Table 2** Pathological Characteristics of Three Young Patients With EBV-Positive DLBCL

| Case | Appearance    | CD20 | CD10 | BCL-6 | MUM1/IRF4 | Ki-67      | EBER    |
|------|---------------|------|------|-------|-----------|------------|---------|
| 1    | Pleomorphic   | +    | —    | —     | +         | 80%        | + (30%) |
| 2    | Centroblastic | +    | —    | +     | +         | >90%       | + (10%) |
| 3    | Centroblastic | +    | —    | —     | +         | 80% to 90% | + (10%) |

Abbreviations: + = positive; — = negative; DLBCL = diffuse large B-cell lymphoma; EBER = EBV-encoded RNA; EBV = Epstein-Barr virus.

review for this study. Lineage was determined by immunohistochemical evaluation using antibodies specific for CD20 (Dako, Carpinteria, CA; dilution 1:100), CD10 (Novocastra, Newcastle-upon-Tyne, UK; dilution 1:100), BCL6 (Dako; dilution 1:10), MUM1/IRF4 (Santa Cruz Biotechnology, Santa Cruz, CA; dilution 1:200), and EBV LMP-1 (Dako; dilution 1:100).

After approval was received from the Institutional Review Board, the presence of EBV-encoded RNA (EBER; Dako) was assessed in all cases using a chromogenic in situ hybridization (CISH) technique. EBER positivity was defined as nuclear expression of EBER by  $\geq 10\%$  of the malignant cells.

For EBER-positive cases, clinical data was obtained from the medical records including age, sex, past medical history, presence of B symptoms, Ann Arbor stage, extranodal involvement, age-adjusted International Prognostic Index (aalPI) score, therapy received, response to therapy, final outcome, survival in months, and cause of death. Laboratory data included complete blood count (CBC), basic metabolic panel (BMP), liver function tests (LFTs), lactate dehydrogenase (LDH), beta-2-microglobulin ( $\beta 2M$ ), and immunoglobulin (Ig) levels. Additional studies included antinuclear antibody (ANA) titers, serologic tests for HIV, human T-cell lymphotropic virus type 1 (HTLV-1), and hepatitis B and C viruses.

## Results

From a total of 137 untreated patients with newly diagnosed DLBCL, not otherwise specified, 20 (15%) patients had nuclear EBER in  $\geq 10\%$  of the malignant cells, and 3 (2.2%) patients were younger than 50 years of age. A summary of the clinical findings is shown in Table 1. There were two men and one woman, 25, 34, and 34 years of age, respectively. None of the patients had a personal history of recurrent dermatologic or sinopulmonary infections, lymphomas, autoimmune conditions, or prior immunosuppressive therapy. All the patients had normal IgG, IgA, and IgM levels as well as negative serology tests for HIV, hepatitis B and C viruses and HTLV-1. ANA testing was negative. None of the patients had hepatosplenomegaly or findings consistent with hemophagocytic syn-

drome. One patient had a retroperitoneal mass with bilateral inguinal lymphadenopathy (stage IIA), one patient had a bulky mediastinal mass (stage IIIB), and one patient had bilateral cervical lymphadenopathy as well as a 4-cm mass in the retroperitoneum (stage IIIB). The serum LDH level was elevated in all patients. The aalPI score was 1 in one patient and 3 in two patients. The patients were treated with combination chemotherapy including rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in case 1, CHOP in case 2, and cyclophosphamide, vincristine, and prednisone (CVP)/CHOP in case 3. Two patients died, at 3 and 13 months, respectively, and one patient was alive at last follow-up examination at 59 months.

The pathologic findings are summarized in Table 2. The neoplasms were composed of sheets of large cells that were centroblastic in two cases and pleomorphic in one case. All tumors were strongly positive for CD20 and MUM1/IRF4, and were negative for CD10, supporting a non-germinal center cell immunophenotype using the Hans algorithm.<sup>14</sup> BCL-6 was positive in one case. The proliferation rate was high, with Ki-67-positive cells being 80% to 90% in all cases. All our cases expressed LMP-1 in  $> 30\%$  of the malignant cells. EBER was positive in 30% of the neoplastic cells in case 1 and 10% of the neoplastic cells in cases 2 and 3. A representative case history is included.

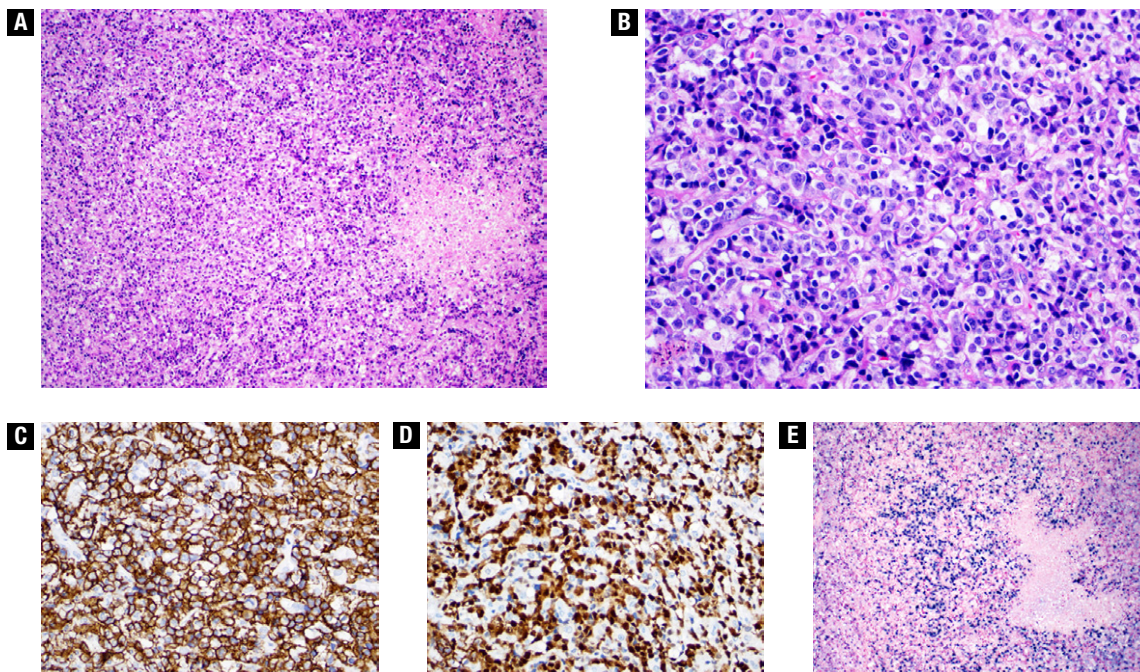
### Case 1

A 25-year-old man presented with a 2-month history of abdominal pain. He denied B symptoms and had a Eastern Cooperative Oncology Group performance status of 0. On physical examination, no peripheral lymphadenopathy was identified, but he had diffuse abdominal pain to deep palpation without rebound. His CBC, BMP, and LFTs were within normal limits. His LDH was 507 IU/L (upper normal level: 400 IU/L) and  $\beta 2M$  was 1.2 mg/L (normal range, 0.78 to 1.47 mg/L). A computed tomography scan revealed a bulky 10-cm retroperitoneal tumor and bilateral inguinal nodes of 1.5 cm in diameter. Morphologically, there was a diffuse effacement of the architecture (Figure 1A) caused by large pleomorphic cells.



## EBV DLBCL in Young People

**Figure 1** (A) Lymph Node Displaying a Diffuse Effacement of the Nodal Architecture With Focal Necrosis (Hematoxylin and Eosin Stain, Original Magnification  $\times 100$ ). (B) Neoplastic Cells Are Large With Centroblastic and Immunoblastic Morphology and Central, Prominent Nucleoli (Hematoxylin and Eosin Stain, Original Magnification  $\times 400$ ). (C) CD20 Immunohistochemistry Shows That the Majority of Neoplastic Cells Are Positive (Original Magnification  $\times 400$ ). (D) MUM-1 Immunohistochemistry Shows That the Majority of Neoplastic Cells Display Nuclear Reactivity (Original Magnification  $\times 400$ ). (E) EBV-encoded RNA (EBER) In Situ Hybridization Shows That Approximately 30% of Neoplastic Cells Are Positive. Extensive Necrosis Is Also Noted (Original Magnification  $\times 100$ )



Scattered Reed-Sternberg-like cells and immunoblasts were noted (Figure 1B). Necrosis was variable, and in some areas was extensive. Immunohistochemical studies showed that the neoplastic cells were positive for CD20 (Figure 1C) and MUM1/IRF-4 (Figure 1D), but negative for BCL6 and CD10, consistent with a non-germinal center phenotype. The proliferation rate as determined with Ki-67 immunostain showed that 80% of the neoplastic cells were positive. EBER CISH showed positivity in 30% of the malignant cells (Figure 1E). A bone marrow biopsy was negative for lymphomatous involvement. EBV DNA in plasma measured by reverse transcriptase polymerase chain reaction was positive with 56.7 copies/ $\mu\text{L}$ . The patient was diagnosed with a bulky stage IIA EBV-positive DLBCL with a low-intermediate risk aaIPI (1/3) and received R-CHOP administered every 21 days for six cycles, achieving a complete response. This was followed by adjuvant radiotherapy (4500 CGy) to the primary tumor site. Ten months later, the patient presented with retroperitoneal and mesenteric lymphadenopathy. He did not receive second-line therapy because of poor performance status, and he died secondary to sepsis and progression of disease.

## Discussion

In this study, we present complete clinical information on three patients who were younger than 50 years old, apparently immuno-

competent, with EBV-positive DLBCL. These three patients had clinically or pathologically aggressive neoplasms and two patients died at 3 months or 13 months despite combination chemotherapy.

Except for not meeting the age cutoff of  $> 50$  years in age, these patients would have otherwise fit with the EBV-positive DLBCL of the elderly entity, included in the 2008 WHO classification.<sup>13</sup> Although the original descriptions of this entity were mainly in patients who were older than 50 years, subsequent reports make reference to this disease occurring in younger patients. For example, in the largest study in this topic, Oyama et al excluded seven patients younger than 40 years of age (7% of their EBV-positive DLBCL patients), and apparently the patients did not have any evidence of immunodeficiency.<sup>15</sup> Because the investigators did not specify the number of patients with EBV-positive DLBCL who were younger than 50 years, it is suggested that there were more than 7%. Additionally, a European series of eight patients with EBV-positive DLBCL by Hoeller et al excluded two patients who were younger than 50 years, representing an incidence of 20% of all their EBV-positive DLBCL cases.<sup>16</sup> Finally, a report from Korea by Park et al found that 41% of their patients with EBV-positive DLBCL were younger than 60 years, and patients as young as 20 years were included.<sup>17</sup> However, lack of immunosuppression was not one of the criteria used for in-

clusion in their study. Our experience with EBV-positive DLBCL has been published previously.<sup>18</sup> In that study, 11 immunocompetent patients were diagnosed with EBV-positive DLBCL, of which 1 patient was younger than 50 years, accounting for an incidence of 9%. In the present study, we identified three patients among 137 patients with DLBCL with EBV-positive DLBCL who were younger than 50 years.

Although not entirely elucidated, the physiopathology of EBV-positive DLBCL of the elderly is thought to reflect chronic EBV infection and immunosenescence, among other less known factors.<sup>19</sup> EBV infection induces upregulation of BCL2 and MYC, genes associated with antiapoptosis and cell proliferation, respectively.<sup>19</sup> On the other hand, Oyama et al found EBV latency patterns II and III associated with EBV-positive DLBCL of the elderly.<sup>15</sup> These patterns have been associated with lymphomas found in profoundly immunosuppressed individuals. Hence, it is difficult to explain the presence of EBV-positive DLBCL in younger, immunocompetent patients. However, other EBV-associated disorders such as classic Hodgkin lymphoma and Burkitt lymphoma are also found in younger patients. Interestingly, in a recent study of 11 patients with EBV-positive DLBCL, there was evidence that the immune system was intact as determined by cell proliferation rates and interferon secretion by T-cells, arguing against the potential role of immunosenescence.<sup>20</sup> Therefore, other factors should be considered in the pathogenesis and incidence of EBV-positive DLBCL. For example, although some studies have shown a higher incidence of EBV-positive DLBCL of the elderly in Asian<sup>15,17</sup> and Hispanic<sup>18</sup> than in Western populations,<sup>16,21</sup> others have not. A recent study detected a 1% to 3% incidence of EBV-positivity among Japanese patients with DLBCL, which is similar to Western populations.<sup>22</sup> This could be explained by geographical location, different strains of EBV, or possibly EBV-specific human leukocyte antigen–modulated susceptibility. Additional studies are needed to clarify these hypotheses.

We acknowledge that in the reported cases of EBV-positive DLBCL of the elderly, most cases have EBV-infected cells in the majority of neoplastic cells, as described in one of our cases; however, current literature does not establish a definitive cutoff. Our series shows that two of our cases had < 20% EBV-positive neoplastic cells, and we wonder if this excludes the diagnosis of EBV-positive DLBCL. We believe there is currently no evidence that the percentage of infected cells determines a difference in the diagnosis or outcome of EBV-positive DLBCL. Further studies, such as testing for the type of latency infection, including testing for LMP-1 and EBNA-2, may be more meaningful to establish the significance of EBV-infected cells in EBV-positive DLBCL in young individuals. We were not able to evaluate the EBV latency patterns in our patients, although our three cases were positive for the expression of LMP-1 in the malignant cells.

From prior studies, EBV positivity was associated with a worse survival rate in patients with DLBCL.<sup>15,17,18</sup> Because these studies were performed for patients who were treated with chemotherapy without rituximab, it is likely that the addition of rituximab to chemotherapy will improve the outcome and survival rate in patients with EBV-positive DLBCL. In a recent report, four of six patients (67%) with EBV-positive DLBCL of the elderly that was treated with chemoimmunotherapy achieved a complete response; however,

from these patients, three (50%) died with disease progression, two (33%) are alive with disease, and only one patient (17%) is alive without disease.<sup>23</sup> A similar outcome was reported in a recent Japanese study, among 16 EBV-positive and 204 EBV-negative DLBCL patients.<sup>22</sup> In that study, the majority of patients received rituximab-containing regimens, suggesting that the addition of rituximab removes the effect of EBV among patients with DLBCL. Larger prospective and/or randomized studies evaluating the effect of EBV infection in DLBCL are needed. If EBV-positive DLBCL proves to carry a worse prognosis than EBV-negative DLBCL in the rituximab era, then there is a potential need for development of EBV-directed therapy. Several preliminary studies have shown potential benefits with EBV-directed cytotoxic T-cells,<sup>24</sup> bortezomib,<sup>25</sup> statins,<sup>26</sup> arginine butyrate, and antivirals,<sup>27</sup> among other therapeutic modalities.

In conclusion, EBV-positive DLBCL can occur in individuals younger than 50 years of age without apparent immunodeficiency, and is associated with aggressive clinical and/or pathologic features. Further studies are necessary to better understand the pathogenetic, predictive, and prognostic roles of EBV in EBV-positive DLBCL to improve therapeutic approaches in this subset of patients. We also suggest that the definition of this disease be revised to allow inclusion of patients younger than 50 years of age, and that the current designation should be modified in future versions of the WHO classification to either EBV-positive DLBCL in immunocompetent individuals or EBV-positive DLBCL in young people.

## Disclosure

The authors have no conflicts of interest.

## References

1. Swerdlow S, Campo E, Harris N, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC; 2008.
2. Armitage JO. The changing classification of non-Hodgkin's lymphomas. *CA Cancer J Clin* 1997; 47:323-5.
3. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993; 329: 987-94.
4. Meyer PN, Fu K, Greiner TC, et al. Immunohistochemical methods for predicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. *J Clin Oncol* 2011; 29:200-7.
5. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med* 2002; 346:1937-47.
6. Chen W, Houldsworth J, Olshen AB, et al. Array comparative genomic hybridization reveals genomic copy number changes associated with outcome in diffuse large B-cell lymphomas. *Blood* 2006; 107:2477-85.
7. Malumbres R, Sarosiek KA, Cubedo E, et al. Differentiation stage-specific expression of microRNAs in B lymphocytes and diffuse large B-cell lymphomas. *Blood* 2009; 113:3754-64.
8. Hecht JL, Aster JC. Molecular biology of Burkitt's lymphoma. *J Clin Oncol* 2000; 18:3707-21.
9. Castillo J, Pantanowitz L, Dezube BJ. HIV-associated plasmablastic lymphoma: lessons learned from 112 published cases. *Am J Hematol* 2008; 83:804-9.
10. Kanavaros P, Briere J, Emile JF, et al. Epstein-Barr virus in T and natural killer (NK) cell non-Hodgkin's lymphomas. *Leukemia* 1996; 10 (suppl 2): s84-7.
11. Anagnostopoulos I, Hummel M, Finn T, et al. Heterogeneous Epstein-Barr virus infection patterns in peripheral T-cell lymphoma of angioimmunoblastic lymphadenopathy type. *Blood* 1992; 80:1804-12.
12. Pallesen G, Hamilton-Dutoit SJ, Rowe M, et al. Expression of Epstein-Barr virus latent gene products in tumour cells of Hodgkin's disease. *Lancet* 1991; 337:320-2.
13. Nakamura S, Jaffe ES, Swerdlow S. EBV positive diffuse large B-cell lymphoma of the elderly. In Swerdlow S, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC; 2008:243-4.
14. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* 2004; 103:275-82.

## EBV DLBCL in Young People

15. Oyama T, Yamamoto K, Asano N, et al. Age-related EBV-associated B-cell lymphoproliferative disorders constitute a distinct clinicopathologic group: a study of 96 patients. *Clin Cancer Res* 2007; 13:5124-32.
16. Hoeller S, Tzankov A, Pileri SA, et al. Epstein-Barr virus-positive diffuse large B-cell lymphoma in elderly patients is rare in Western populations. *Hum Pathol* 2010; 41:352-7.
17. Park S, Lee J, Ko YH, et al. The impact of Epstein-Barr virus status on clinical outcome in diffuse large B-cell lymphoma. *Blood* 2007; 110:972-8.
18. Morales D, Beltran B, De Mendoza FH, et al. Epstein-Barr virus as a prognostic factor in de novo nodal diffuse large B-cell lymphoma. *Leuk Lymphoma* 2010; 51:66-72.
19. Castillo JJ, Beltran BE, Miranda RN, et al. Epstein-Barr virus-positive diffuse large B-cell lymphoma of the elderly: what we know so far. *Oncologist* 2011; 16:87-96.
20. Morishima S, Yamamoto K, Kimura H, et al. Increased peripheral T cell responses to EBV-infected cells with frequent detection of EBV-DNA in plasma and viral mRNA in peripheral B-cells in immunocompetent EBV-positive diffuse large B-cell lymphoma patients. *Blood* 2010; 116:4163 [abstract].
21. Gibson SE, Hsi ED. Epstein-Barr virus-positive B-cell lymphoma of the elderly at a United States tertiary medical center: an uncommon aggressive lymphoma with a nongerminal center B-cell phenotype. *Hum Pathol* 2009; 40:653-61.
22. Beltran BE, Castillo JJ, Salas R, et al. Epstein-Barr virus-positive diffuse large B-cell lymphoma of the elderly treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone: report of two cases from South America. *Leuk Lymphoma* 2011; 52:153-6.
23. Wada N, Ikeda J, Hori Y, et al. Epstein-Barr virus in diffuse large B-Cell lymphoma in immunocompetent patients in Japan is as low as in Western Countries. *J Med Virol* 2011; 83:317-21.
24. Merlo A, Turrini R, Bobisse S, et al. Virus-specific cytotoxic CD4+ T cells for the treatment of EBV-related tumors. *J Immunol* 2010; 184:5895-902.
25. Zou P, Kawada J, Pesnicak L, et al. Bortezomib induces apoptosis of Epstein-Barr virus (EBV)-transformed B cells and prolongs survival of mice inoculated with EBV-transformed B cells. *J Virol* 2007; 81:10029-36.
26. Katano H, Pesnicak L, Cohen JL. Simvastatin induces apoptosis of Epstein-Barr virus (EBV)-transformed lymphoblastoid cell lines and delays development of EBV lymphomas. *Proc Natl Acad Sci U S A* 2004; 101:4960-5.
27. Perrine SP, Hermine O, Small T, et al. A phase 1/2 trial of arginine butyrate and ganciclovir in patients with Epstein-Barr virus-associated lymphoid malignancies. *Blood* 2007; 109:2571-8.