EBV-positive Diffuse Large B-cell Lymphoma, NOS, in a Filipino Patient: Mimickers and Essential Ancillary Studies

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ABSTRACT

Epstein-Barr virus positive diffuse large B-cell lymphoma (EBV+ DLBCL) is prevalent among Asians but is underreported in the Philippine setting. We report the case of an 88-year-old male who presented with difficulty swallowing. CT scan showed an ill-defined soft tissue focus with calcifications in the supraglottic to hypopharyngeal region measuring approximately 2.6 x 1.7 x 1.5 cm, and multiple lymphadenopathies in the head and neck. Biopsy of the masses at the left tonsil, left arytenoid mucosa, pyriform sinus, and aryepiglottic fold showed large lymphoid cells with several Reed-Sternberg-like cells in a background of small lymphocytes, neutrophils, few eosinophils and histiocytes. A panel of immunohistochemical stains and EBER-ish were performed to differentiate among six entities that were morphologically similar to the patient’s case, namely, classic Hodgkin lymphoma, T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), DLBCL, NOS, anaplastic variant, B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic HL (gray zone lymphoma), and infectious mononucleosis (IM). The neoplastic cells expressed CD20, CD30, CD45, PAX5, CD10, MUM-1, BCL6, BCL2, and c-myc, while CD3, CD15 and ALK-1 were negative. The cells of interest also showed nuclear staining (30-40%) on Epstein-Barr virus encoding RNA in-situ hybridization (EBER-ish). The Ki-67 showed a proliferation index of 40-50%. Given the differences in prognosis and treatment among these diseases, judicious use of immunostains and EBER-ish is recommended for accurate diagnosis.

Key words: Immunohistochemistry, Philippines, DLBCL, Epstein-Barr virus, EBV+ DLBCL

INTRODUCTION

Diffuse large B-cell lymphoma, of no special type (DLBCL, NOS) is a neoplasm composed of diffusely growing B lymphocytes with nuclei twice as large as that of normal lymphocytes. Histomorphology and immunohistochemical studies have allowed sub-classifications of DLBCL, aiding in both diagnosis and treatment.1 Epstein-Barr virus positive DLBCL, NOS (EBV+ DLBCL) is one such classification which accounts for 5-15% of DLBCL patients among Asians.2 From the time that it was initially described by Oyama et al in 2003, there have been multiple studies on its prevalence across Asia.2 EBV + DLBCL is further classified into two subtypes: a polymorphic subtype with surrounding reactive infiltrates, and a monomorphic subtype composed of sheets of large cells. These subtypes are important to note because of their close resemblance to other lymphoproliferative neoplasms.3

Despite the increased prevalence of EBV + DLBCL in Asian countries, this entity remains underreported in the Philippine setting. An exhaustive search on Philippine e-journals, HERDIN Plus, and the Philippine Journal of Pathology yielded no reports of EBV + DLBCL. This report aims to add to the body of knowledge on this disease in the local setting, and elucidate a method to differentiate among six morphologically similar entities.

CASE

This is a case of an 88-year-old Filipino, previously healthy male who presented with rapidly worsening
difficulty of swallowing solid food, which started two
weeks prior to consultation. This symptom was associated
with gradual weight loss of approximately 10 kg. There
was no fever, night sweats, chest pain, or difficulty of
breathing. Complete blood count showed the following
result: hemoglobin of 80 g/L, hematocrit of 0.25, white
blood cell count of 8.50 x 10^9/L, and platelet count
of 287 x 10^9/L. Differential count was predominantly
neutrophilic with no immature cells seen. Serum lactate
dehydrogenase (LDH) was normal. Serum EBV level was
not tested. CT scan showed an ill-defined soft tissue focus
with calcifications in the supraglottic to hypopharyngeal
region measuring approximately 2.6 x 1.7 x 1.5 cm, and
prominent, enlarged, round to ovoid lymph nodes at the
submental, left submandibular, right mid-jugulocarotid
and left upper to lower jugulocarotid and posterior
cervical spaces (Figure 1). An F-18 FDG PET scan done a
month later revealed multiple FDG-avid (Lugano Score 5)
lymphadenopathies scattered in the bilateral cervical, right
taxillary, mediastinal, right peribronchial, right subpleural,
peritoneal, omental, mesenteric, retroperitoneal, pelvic
and inguinal regions, with the largest lymphadenopathy
measuring 3.2 x 2.8 cm in greatest dimensions (Figure
2). Laryngoscopy showed masses at the left tonsil, left
tyroid pouch, pyriform sinus, and aryepiglottic fold
which were submitted for histopathologic evaluation.

Microscopic examination showed proliferation of large
lymphoid cells with several Reed-Sternberg-like cells in
a background of small lymphocytes, neutrophils, few
eosinophils and histiocytes. (Figure 5). Using formalin-fixed,
paraffin-embedded tissue sections, immunohistochemical
studies were performed on automated staining platforms
according to the manufacturer’s instructions. The
antibodies used, their dilutions, and respective vendors
were as follows: anti-CD3 (clone 2GV6; Ventana/Roche
Tissue Diagnostics, Tucson, AZ, USA; 1:100); anti-CD10
(clone SP67; Ventana/Roche Tissue Diagnostics, Tucson,
AZ, USA; 1:100); anti-CD15 (clone MMA; Ventana/Roche
Tissue Diagnostics, Tucson, AZ, USA; 1:100); anti-CD20
(clone L26; Ventana/Roche Tissue Diagnostics, Tucson,
AZ, USA; 1:100); anti-CD30 (clone Ber-H2; Ventana/Roche Tissue Diagnostics, Tucson, AZ, USA; 1:100); anti-CD45 (clone RP2/18; Ventana/Roche Tissue Diagnostics, Tucson, AZ, USA; 1:100); anti-PAX5 (clone SP34; Ventana/Roche Tissue Diagnostics, Tucson, AZ, USA; 1:100); anti-MUM-1 (clone MRQ-43; Ventana/Roche Tissue Diagnostics, Tucson, AZ, USA; 1:100); anti-BCL6 (clone G1191E/A8; Ventana/Roche Tissue Diagnostics, Tucson, AZ, USA; 1:100); anti-BCL2 (clone 124; Ventana/Roche Tissue Diagnostics, Tucson, AZ, USA; 1:100); anti-c-myc (clone 9E10; Ventana/Roche Tissue Diagnostics, Tucson, AZ, USA; 1:100); anti-ALK-1 (clone ALK01; Ventana/Roche Tissue Diagnostics, Tucson, AZ, USA; 1:100); and anti-Ki-67 (clone 30-9; Ventana/Roche Tissue Diagnostics, Tucson, AZ, USA; 1:100). Epstein-Barr encoding region in-situ hybridization (EBER-ish) was performed using EBER probe (Leica BONDMAX, Leica Biosystems, Buffalo Grove, IL, USA), using the built-in protocol from the manufacturer.

The large lymphoid cells as well as the Reed-Sternberg-like cells expressed CD45, CD20, PAX5, CD30 (30%), CD10 (60%), BCL6 (30%), MUM-1 (80%), BCL2 (20%), and c-myc (10%), while CD3, CD15 and ALK-1 were negative. The cells of interest also showed nuclear staining (30-40%) on Epstein-Barr encoding region in-situ hybridization (EBER-ish). The Ki-67 showed a proliferation index of 40-50% (Figure 4). Based on the morphology and the

Figure 3. (A and B) The tumor is composed of sheets of large lymphoid cells surrounded by small lymphocytes, neutrophils, few eosinophils and histiocytes. There are also many scattered Reed-Sternberg-like cells showing irregularly shaped nuclei, prominent nucleoli, and scant basophilic cytoplasm (H&E, 40x).

Figure 4. The large cells and Reed-Sternberg-like (RS-like) cells were positive for LCA (A), CD20 (C), and PAX5 (F) (40x). Some of the large cells and RS-like were positive for CD30 (30%) (D). The tumor cells also expressed CD10 (30%) (G), BCL6 (30%) (H) and MUM-1 (80%) (I) (20x). The immunostains for CD3 (B), CD15 (E), and ALK-1 (J) were negative (40x). Ki-67 shows a high (40-50%) proliferation index (K) (20x). Approximately 30-40% of the large cells showed nuclear staining on Epstein-Barr encoding region in-situ hybridization (L) (20x).
immunoprofile, this case was thus signed out as an EBV+ DLBCL, NOS.

DISCUSSION

EBV is one of the first oncogenic viruses to be identified. It is oncogenic partly due to its link with immuno-suppression and chronic antigenic activation. Worldwide, EBV infection has a prevalence ranging between 80-95%. It is more commonly associated with nasopharyngeal carcinoma and Burkitt lymphoma, though it is not rarely linked with various other tumors.

EBV+ DLBCL has a higher prevalence in Asia than in Europe and America (Table 1). In the Philippines, there have been published studies documenting lymphomas in general, but no recent literature focusing on DLBCL, EBV positive or otherwise. A 2004 study of various cases of lymphoma at a tertiary hospital showed a greater prevalence of non-Hodgkin lymphoma (NHL) as compared to Hodgkin lymphoma (HL), involving a median age of 29 years and most often involving the neck. Most of the cases were Stage IIA on diagnosis. One study done more than a decade ago reported few cases of EBV+ HL, but not EBV+ DLBCL. It is postulated that genetic factors (e.g., HLA types) and EBV strains play a role in the regional differences in EBV prevalence.

Various studies across many populations report the median age of DLBCL to be 70 years, with higher incidence in males and in developing countries. A similar trend is observed with EBV+ DLBCL. There have been reports of this entity appearing over a wide range of ages, though it is less common and carries a better prognosis among younger patients; thus, the “elderly” designation in EBV+ DLBCL was removed in the 2017 edition of the WHO classification guidelines. Immunosenesence, which comes with aging, might explain the higher prevalence of EBV+ DLBCL and related diseases among the elderly. It involves dysregulation of the T-cell response, loss of immune surveillance, deficiencies in cytokine production, and anergic memory cells.

Majority of EBV+ DLBCL patients present with extranodal masses (particularly in the tonsils, skin, lungs, and gastrointestinal tract) and lymphadenopathy. Around 60% of patients present with B symptoms, such as fever, night sweats, and weight loss. LDH levels are often increased. EBV+ DLBCL predominantly presents with a mixed proliferation of large transformed cells, immunoblasts and Reed-Sternberg-like cells, in a background of plasma cells, plasmablasts, histiocytes, epithelioid cells and small lymphocytes. This polymorphic pattern, as is seen in this case, can resemble T-cell/histiocyte-rich large B-cell lymphoma (T(H)RBLCL) or classic HL. Geographical areas of necrosis or angioinvasion may or may not be present. A monomorphic subtype has also been described, composed of sheets of large cells, which may be difficult to differentiate from EBV negative DLBCL, without immunohistochemical studies.

The similarity of morphologic features between EBV+ DLBCL and other lymphomas presents a diagnostic difficulty. Other considerations based on morphology and clinical presentation included T-cell/histiocyte-rich large B-cell lymphoma (T(H)RBLCL), DLBCL, NOS, anaplastic variant, and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic HL (gray zone lymphoma). A benign entity, infectious mononucleosis (IM), was also considered. Various immunohistochemical studies were employed to identify the type of tumor from among its morphologically similar counterparts. A comparison of the immunoprofile of this case and the differential diagnoses is presented in Table 2.

On the initial panel, a B-cell origin was considered due to strong expression of CD20 in the large cells and RS-like cells, and negative CD3. The Ki-67 indicated a moderate to high proliferation index. The Ki-67 indicated a moderate to high proliferation index. Among the known B-cell lymphomas, these five entities were selected as differential diagnoses due to the common feature of large B cells and occasional RS-like cells, surrounded by different types of reactive cells, with moderate to high proliferation index. Four of these entities are also more prevalent among elderly males as in this case. Clinically, these entities present with nodal or extranodal masses, with or without lymphadenopathies, with gray zone lymphoma being the exception.

Morphologically, one of the leading considerations was classic Hodgkin lymphoma, particularly the mixed cellularity subtype. This is the most common subtype in developing countries. It is noted that mixed cellularity CHL resembles the polymorphic subtype of EBV+DLBCL. The strong positivity of PAX-5, and CD45 in this case, usually has a slower progression and is often nodal in presentation. THRLBCL is characterized by large B cells, surrounded by small T-cells and histiocytes. However, it is defined as having neoplastic cells occupying <10% of the cell population. EBER-ISH is also mostly negative in

Table 1. Prevalence of EBV+ DLBCL among different countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Age groups studied</th>
<th>Sample</th>
<th>% prevalence</th>
<th>EBER cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>Elderly &gt;50</td>
<td>25/141</td>
<td>18%</td>
<td>20%</td>
</tr>
<tr>
<td>China</td>
<td>Elderly &gt;50</td>
<td>18/260</td>
<td>6.9%</td>
<td>30%</td>
</tr>
<tr>
<td>Korea</td>
<td>Elderly &gt;50</td>
<td>19/147</td>
<td>13%</td>
<td>50%</td>
</tr>
<tr>
<td>Germany</td>
<td>Elderly &gt;50</td>
<td>1/185</td>
<td>0.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Elderly &gt;50</td>
<td>8/258</td>
<td>3.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Mexico</td>
<td>Elderly &gt;60</td>
<td>9/136</td>
<td>7%</td>
<td>“majority”</td>
</tr>
<tr>
<td>United States</td>
<td>Elderly &gt;60</td>
<td>5/95</td>
<td>5.3%</td>
<td>None; at least 80% of cells in tumors considered positive</td>
</tr>
</tbody>
</table>
This entity. Gray zone lymphoma has variable histologic features; the main criteria is that the immunohistochemical profiles are not consistent with what is expected from the morphology. There is a morphologic and immunoprofile overlap between cHL and DLBCL. In this case, the morphology suggests cHL, but immunohistochemical profile most closely matches DLBCL, NOS, which makes gray zone lymphoma a possible diagnosis. However, this disease mostly presents in young to middle aged patients, and often occurs in the mediastinum. EBER-ISH is also frequently negative in gray zone lymphoma. It is known that EBV+ DLBCL is usually of non-germinal center B-cell origin, however, in a study done by Lu et al., at least 11.5% of EBV+ DLBCL cases were CD10 positive.6

A similar dilemma was discussed in a case report by Wang and colleagues, describing a tumor that was histologically similar to DLBCL, classic HL, and gray zone lymphoma. The study used other techniques not readily available in the Philippine setting, such as OCT2 and BOB1 immunostains; however, a definite diagnosis was still not established. It was proposed that EBV is associated with lymphomas that may not fit neatly into WHO classifications or IHC-driven categorizations.19

A non-neoplastic differential, though no less important, is infectious mononucleosis (IM). While it is observed more often in younger patients, it can present in older age and be mistaken for malignancy. IM presents clinically with fever, pharyngitis, and cervical to generalized lymphadenopathy in 50% of patients. Immunoblasts are increased, sometimes forming sheets, which can stain positive for CD50 and CD45, like in this patient. There can also be large, mono- multinucleated cells with prominent nucleoli, which can be mistaken for Reed-Sternberg or Hodgkin cells. However, in IM, there is relatively preserved follicular architecture, and the background is polymorphous and composed mostly of small T-lymphocytes (CD3+ and CD8+).20 BCL2 and BCL6 are also negative in IM.21

Ancillary studies to differentiate reactive from neoplastic hematolymphoid entities include flow cytometry to determine the clonality of populations through light chain restriction, morphologic assessment of light chain Kappa/Lambda mRNA ratio with CISH, and/or detection of gene rearrangements in BCL2, BCL6 and MYC with FISH.21,22

A clonal IGH and/or IGK gene rearrangement by Southern blot, polymerase chain reaction, or next-generation sequencing will also support the diagnosis of a B-cell neoplasm. However, molecular methods are only necessary if the histologic and immunohistochemical features are equivocal.23

There have also been some studies done, further detailing the genomic features of EBV+DLBCL and other lymphomas using next generation sequencing, gene expression profiling and other molecular methods. It may be useful in the future, once these technologies are more widely available.24,25

**Table 2. Comparison of immunohistochemical findings in the patient and differential diagnoses**

<table>
<thead>
<tr>
<th>IHCs</th>
<th>Patient Classic Hodgkin Lymphoma</th>
<th>T-cell/histyocyte-rich large B-cell</th>
<th>B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic HL</th>
<th>EBV+ DLBCL, NOS</th>
<th>DLBCL, NOS</th>
<th>Infectious mononucleosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3</td>
<td>Negative</td>
<td>Negative, but (+) in 10% of cases</td>
<td>Negative in large neoplastic cells; (+) in T cells in background</td>
<td>Negative</td>
<td>Negative</td>
<td>(+) in surrounding small cells</td>
</tr>
<tr>
<td>CD20</td>
<td>(+)</td>
<td>Variable positive and weak in 20-40% of cases</td>
<td>(+) in large neoplastic cells; (+) strong in cases that resemble cHL; (+) in cases that resemble DLBCL</td>
<td>(+)</td>
<td>(+)</td>
<td>(+), can be dim if with plasmacytoid differentiation</td>
</tr>
<tr>
<td>Ki-67</td>
<td>40-50%</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>40-90% Moderate to high</td>
</tr>
<tr>
<td>PAX5</td>
<td>(+) strong</td>
<td>Weakly positive; negative in 10% of cases in nodular lymphocyte-predominant HL</td>
<td>(+) strong in large neoplastic cells</td>
<td>(+) strong</td>
<td>(+) strong</td>
<td>(+) in immunoblasts</td>
</tr>
<tr>
<td>CD15</td>
<td>Negative</td>
<td>[-], Negative in 35-25%, usually in nodular lymphocyte-predominant</td>
<td>(+) in cases that resemble DLBCL; (+) in cases that resemble cHL</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>ALK-1</td>
<td>Negative</td>
<td>(+) 30%</td>
<td>(-)</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>CD10</td>
<td>(+) 30%</td>
<td>Negative</td>
<td>(-)</td>
<td>(+/-), usually weak and partial</td>
<td>(+) only 10-20% and anaplastic</td>
<td>(+) in immunoblasts</td>
</tr>
<tr>
<td>BCL6</td>
<td>(+) 30%</td>
<td>(-)</td>
<td>(+) Variable</td>
<td>Negative</td>
<td>(+) 60-90%</td>
<td>Negative</td>
</tr>
<tr>
<td>BCL2</td>
<td>(+) 20%</td>
<td>(+) Variable</td>
<td>(+) Variable; (+) Infrequent; (+) Variable [criteria: 50% or more of cells]</td>
<td>Negative</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>c-myc</td>
<td>(+) 10%</td>
<td>(+) Variable</td>
<td>(+) Variable; (+) Infrequent; (+) Variable [criteria: 40% or more of cells]</td>
<td>Negative</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>EBER-ISH</td>
<td>(+) 30-40%</td>
<td>Rarely positive; often positive in mixed-cellular and lymphocyte-depleted (75% of cases)</td>
<td>Negative (positive in 15%); (+); arbitrary cutoff of 20-40% of cells.</td>
<td>Negative</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>CD45</td>
<td>(+)</td>
<td>Negative</td>
<td>(+) in nodular lymphocyte-predominant; (+) in large neoplastic cells; (+), focally Negative; (+) Variable</td>
<td>(+)</td>
<td>(+) 35-65% of cases with plasmacytoid differentiation</td>
<td>(+)</td>
</tr>
<tr>
<td>MUM-1</td>
<td>(+) 80%</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

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The prognosis and appropriate treatment of EBV+ DLBCL is markedly different between these closely related entities. EBV positivity is associated with more advanced stage, extranodal involvement, and poorer response to treatment.

Although lymphomas in general are chemosensitive, the exact chemotherapeutic regimen to be used will differ according to the specific type. HL generally involves adjacent nodes in the same anatomic site, and typically spreads to adjacent nodal areas; isolated deposits in distant nodes is rare. Combination chemotherapy consisting of doxorubicin, vinblastine, bleomycin, and dacarbazine (ABVD) is typically given, and a scoring system is currently in use to determine patient’s prognosis. The International Prognostic Score (IPS) is the most commonly used risk stratification system for this disease, and is highly predictive of freedom from disease progression. This includes clinical and laboratory parameters such as gender, serum albumin, hemoglobin, stage, age, white blood cell count, and lymphocyte count. Initial treatment with chemotherapy, with or without radiotherapy, generally results in cure.

Gray zone lymphoma is a rare neoplasm that has a more aggressive course with poorer outcomes. This typically presents in males, and is more often diagnosed at an advanced stage. There are currently no standard management guidelines for gray zone lymphoma. However, a prospective study has found that these patients typically respond to a combination regimen consisting of dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R), with 62% of patients achieving continuous complete remission.

Patients with NHL typically present with painless peripheral lymphadenopathy. This may or may not be accompanied by B symptoms. DLBCL is the most common histologic subtype of NHL, accounting for around 31% of this disease. Prognosis for this disease depends on histology and clinical parameters rather than stage, and a scoring system is currently being used to determine prognosis. The International Prognostic Index (IPI) identified age, serum LDH, performance status, stage, and extranodal involvement to be predictive of survival. Combination therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone, with or without rituximab (R-CHOP), is the first-line treatment. The treatment strategies of EBV+ DLBCL currently follow that of other DLBCL; however, clinical trials involving activation of lytic viral genes that will render tumor cells susceptible to antiviral treatment are currently being studied. Other therapeutic methods under study include boosting the anti-viral immune response with vaccines or EBV-specific cytotoxic lymphocytes.

Although the previously discussed entities involve lymphohematopoietic tissues, their biologic and clinical behaviors are distinct. It is therefore imperative that an accurate histopathologic diagnosis is made in order to determine the correct treatment strategy for these patients.

CONCLUSION

EBV+ DLBCL should be considered as a differential diagnosis in immunocompetent patients presenting with rapidly enlarging extranodal masses and multiple lymphadenopathies, especially if histologic examination of the mass reveals RS-like cells in a reactive background. It is also important to perform immunohistochemical studies and EBER-ISH to attain a specific diagnosis. It is recommended that clinicians and pathologists test for and report EBV positivity in cases of lymphoma as this affects prognosis and treatment.

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