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LETTER TO THE EDITOR

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

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Epstein–Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL) of the elderly is a novel entity included in the World Health Organization (WHO) classification of hematopoietic and lymphoid tumors [1]. EBV-positive DLBCL of the elderly is a very aggressive disease that occurs more frequently in patients older than 50 years and presents with frequent extranodal involvement and the presence of EBV in tumoral cells. The prognosis is poor and the survival is short [2]. A few studies have reported lower response rates to conventional anthracycline-based chemotherapy in comparison with responses seen in EBV-negative patients with DLBCL [2,3], but there are no data on EBV-positive DLBCL of the elderly treated with rituximab in combination with chemotherapy. In this letter, we present two cases of EBV-positive DLBCL of the elderly with a good initial response to the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

Our first case is a 74-year-old man without a significant past medical history and an Eastern Cooperative Oncology Group (ECOG) performance status of 1. One week prior to admission, he developed progressive colicky abdominal pain and bloating. He denied B symptoms. An intestinal obstruction was suspected and a 4×4 cm ileal mass was identified. The patient underwent a partial ileal resection. Pathological studies revealed a lymphoproliferative process with monomorphic appearance and scattered areas of necrosis. Based on immunohistochemical studies, the sample was most consistent with a CD20-positive diffuse large B-cell lymphoma with a non-germinal center (NGC) phenotype (CD10 negative, BCL6 negative, and MUM1 positive). Expression of CD30 and BCL2 was negative, and Ki67 expression was 80%. EBV-encoded RNA (EBER) *in situ* hybridization (ISH) was positive in the tumoral cells (Figure 1). Further staging showed a 2 cm mass in the lower lobe of the right lung. A bone marrow biopsy was negative for lymphomatous involvement, and lactate dehydrogenase (LDH) levels were within normal limits. The patient was diagnosed with stage IVA EBV-positive DLBCL of the elderly. His International Prognostic Index (IPI) score was 3. The patient received six cycles of R-CHOP administered every 21 days with growth factor support. At the end of treatment, there was no evidence of disease. Unfortunately, 12 months after his initial diagnosis, the patient presented with seizures, and a computed tomography (CT) scan of the brain showed multiple parenchymal lesions consistent with relapsed lymphoma. The patient underwent brain irradiation with radiological

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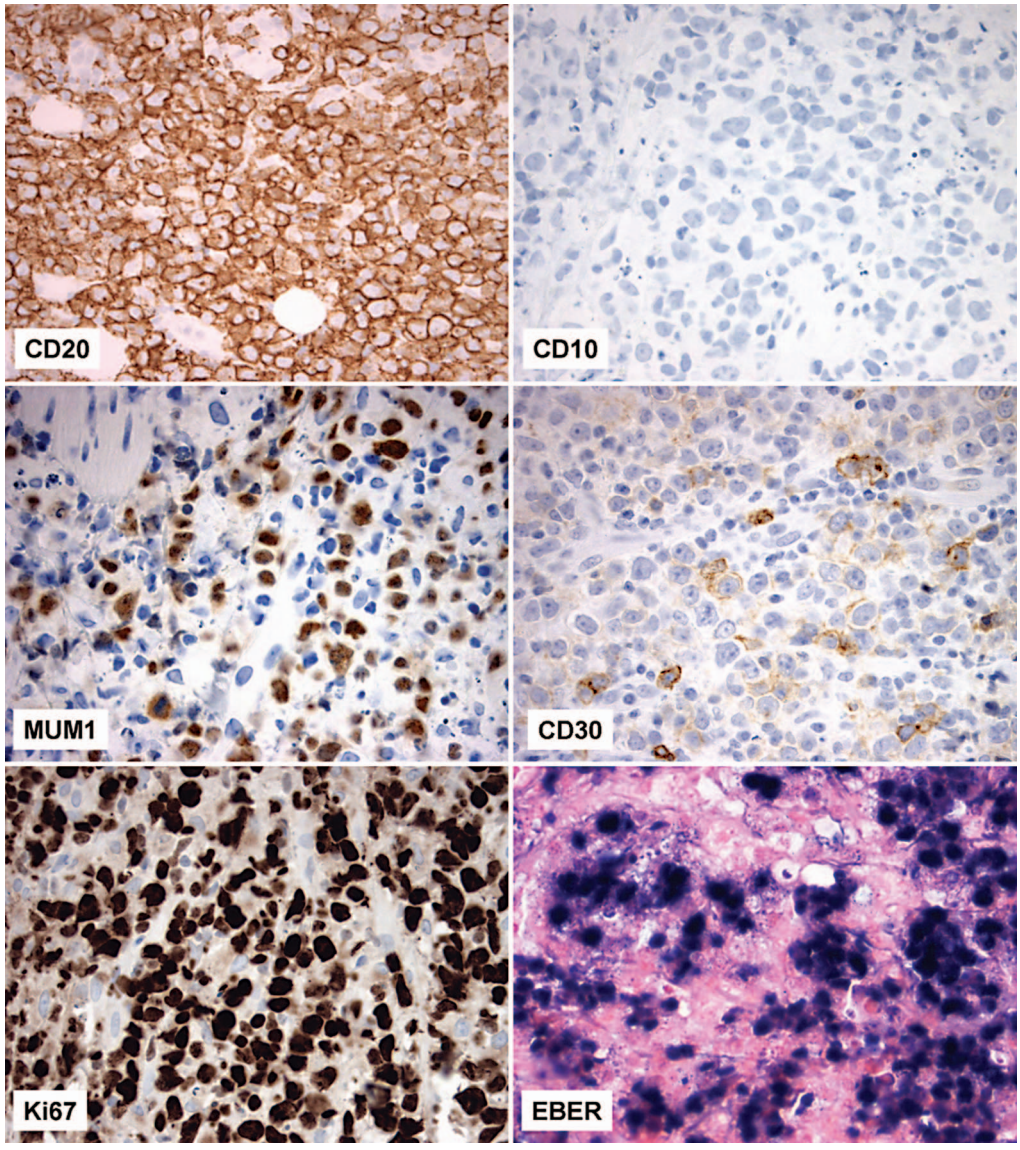

Figure 1. Immunohistochemical profile of a patient with EBV-positive diffuse large B-cell of the elderly. The case shows a strong expression of CD20, Ki67 and EBER. The MUM1-positivity and CD10-negativity confers this lymphoma a non-germinal center origin.

response, but 3 months later presented with a new 5 cm brain lesion. He died shortly thereafter without evidence of systemic disease.

The second case is a 73-year-old man without a significant past medical history and an ECOG performance status of 0. He presented with a 3-month course of a lump in the right side of the throat and ipsilateral swollen lymph nodes. He denied B symptoms. In the physical examination, a 2 cm mass was visualized in the right tonsil and a 3 × 3 cm right cervical lymph node was identified. LDH levels were within normal limits. A biopsy of the tonsil showed a monomorphic CD20-positive diffuse large B-cell lymphoma with minimal necrosis and a NGC phenotype (CD10 negative, BCL6 negative, and MUM1 positive). Additional immunohistochemical studies showed CD30 negativity and BCL2 positivity with a Ki67 expression of 70%. By ISH, there was expression of EBER in most of the tumoral cells (>80%). Additional imaging and a bone marrow biopsy did not show additional lymphomatous involvement. The patient was diagnosed with a stage IIA EBV-positive DLBCL of the elderly with an IPI score of 1. He received six cycles of R-CHOP given every 21 days. By CT scan, the patient showed a complete response; he continues in remission 12 months after his diagnosis.

In 2007, Oyama and colleagues reported 96 cases of patients with B-cell lymphomas that expressed EBER [2]. When compared to EBV-negative patients, EBV-positive patients were older, and a larger proportion had poor performance status, the presence of B symptoms, and lower response rates to chemotherapy. Additional evaluation showed that

Table I. Clinical characteristics of patients with EBV-positive DLBCL of the elderly treated with R-CHOP.

Cases	Age (years)	Sex	Location	IPI score	Treatment	Response	Outcome	Survival
Gibson [8]	60	M	Multicentric LAD	High-intermediate	R-CHOP	PR	AWD	1 month after 2nd line R-ICE
	79	F	Multicentric LAD	High-intermediate	R-CHOP	PD	DWD	1 month
	68	M	Multicentric LAD	High	R-CHOP	CR	DWD	20 months
	63	M	Multicentric LAD	High	R-CHOP	CR	AWD	3 months after 2nd line R-ICE followed by HSCT
Present report	74	M	Ileal mass and mesenteric LAD	High-intermediate	R-CHOP	CR	DWD	15 months
	73	M	Right tonsil and right cervical LAD	Low	R-CHOP	CR	AWOD	12 months

EBV, Epstein–Barr virus; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; PR, partial response; PD, progressive disease; IPI, International Prognostic Index; LAD, lymphadenopathy; AWD, alive with disease; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; DWD, died with disease; HSCT, hematopoietic stem cell transplant; AWOD, alive without disease.

Table II. Pathological characteristics of patients with EBV-positive DLBCL of the elderly treated with R-CHOP.

Cases	Morphology	CD20	CD10	BCL6	MUM1	BCL2	CD30	LMO2	Ki67	Ig gene rearrangement
Gibson [8]	Polymorphic	+ (focal)	−	−	+	NR	+	−	95%	ND
	Polymorphic	+ (focal)	−	−	+	NR	NR	−	70%	Monoclonal IgH
	Monomorphic	+	−	+	+	NR	+	−	60%	NR
	Monomorphic	+	−	−	+	NR	+	−	70%	NR
Present report	Monomorphic	+	−	−	+	−	−	ND	80%	Monoclonal IgH
	Monomorphic	+	−	−	+	+	−	ND	70%	ND

EBV, Epstein–Barr virus; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; Ig, immunoglobulin; ND, not done; NR, not reported.

patients with EBV-positive DLBCL expressed EBNA2, which correlates with a type III EBV latency pattern, similar to post-transplant and human immunodeficiency virus (HIV)-associated B-cell lymphomas [2]. This finding suggested an immunodeficiency, likely associated with immunosenescence and/or chronic EBV infection, as a factor in the pathogenesis of this disease. The prognosis of EBV-positive DLBCL of the elderly is poor, with a median survival of about 2 years [1].

In EBV-positive DLBCL, the response rates to chemotherapy seem lower than in EBV-negative patients. A Japanese study evaluated the role of EBV in primary gastric DLBCL lymphomas that received CHOP. The investigators found that 50% of the chemotherapy-refractory patients had EBV-positive [4]. Similarly, Oyama and colleagues reported complete and partial response rates of 66% vs. 91% and 14% vs. 8%, respectively; this difference was statistically significant [2]. Finally, Park and colleagues found that the overall response rate to initial treatment was significantly lower in patients with EBV-positive compared with EBV-negative DLBCL (72% vs. 92%) [3]. However, the large majority of patients in these reports received CHOP without rituximab.

Oyama and colleagues describe only one case who received chemotherapy combined with rituximab as initial treatment, but further data were not provided [2]. Similarly, Park and colleagues reported that two of the patients in their cohort with EBV-positive DLBCL received rituximab, but no additional data were provided [3]. Since rituximab has been introduced in the treatment of DLBCL, the prognosis has improved considerably, and both progression-free and overall survivals have increased significantly [5–7]. However, experience on EBV-positive DLBCL of the elderly treated with R-CHOP is very limited, and, in a literature search through August 2010, we found four additional cases treated with R-CHOP [8]. Their clinical and pathological characteristics are shown in Tables I and II, respectively. There were three responses to R-CHOP, two complete responses and one partial response. Out of these three patients, one died of relapsed disease 20 months after diagnosis, and the other two patients are alive with disease.

This letter reports a complete response in two patients with EBV-positive DLBCL of the elderly treated with R-CHOP. One patient had an advanced stage with two extranodal sites involved (ileum and lung), and the other had an early stage with a tonsilar primary site. Unfortunately, our patient with

advanced stage relapsed in the brain, 12 months after diagnosis. Of note, both patients reported here showed a NGC immunohistochemical profile (Figure 1). In a prior report from our group, 82% of patients with EBV-positive DLBCL had a NGC profile [9]. Similarly, Park and colleagues reported that 71% of their patients with EBV-positive DLBCL had a NGC profile [3]. Although in the pre-rituximab era, patients with NGC DLBCL had a worse outcome than those with GC DLBCL [10], few studies have shown an improvement in survival in patients with NGC DLBCL with the addition of rituximab to chemotherapy [11–13]. Based on these limited data, one can infer that given the NGC profile of patients with EBV-positive DLBCL of the elderly, they should obtain a benefit with the addition of rituximab to CHOP; however, the prognosis will remain worse than for patients with EBV-negative DLBCL. Novel therapies might be needed to improve the prognosis in these patients.

In summary, we add to the current body of literature by presenting two South American patients with EBV-positive DLBCL of the elderly treated with R-CHOP. This condition seems to affect predominantly men, and to present with a NGC immunohistochemical profile. Our patients achieved a CR with R-CHOP, which is encouraging. However, one of our patients relapsed. Similar situations have been seen in other reports, but data on the response and survival of patients with EBV-positive DLBCL of the elderly with rituximab-containing regimens continue to be rather limited. Larger prospective studies are needed to prove the efficacy of R-CHOP or the potential need of novel therapies in these patients.

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