

Case Study

Age-Related Epstein-Barr Virus-Positive Lymphoproliferative Disorders of the Orbit and Maxillary Sinus : A Case Report

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We report a rare case of age-related Epstein-Barr virus (EBV)-positive B-cell lymphoproliferative disorder (aEBVBLPD) primarily involving the orbit and maxillary sinus. Lesions in the left orbit and maxillary sinus were observed in a 59-year-old man presenting with pain in the left orbit and maxilla. Owing to the presence of Reed-Sternberg-like cells, the initial diagnosis was nodular sclerosis-type Hodgkin's lymphoma. Clinical stage was IIAE, and response to chemotherapy and radiotherapy was favorable. Further immunohistochemical and *in situ* hybridization analyses of the Reed-Sternberg-like giant cells revealed CD30, CD15, CD20, Bob-1, Oct-2, EBV-encoded RNAs (EBERs) and latent membrane protein-1 (LMP-1) expression. The characteristics of the present case, which included immunohistochemical findings, sites of primary lesions, absence of other lymph node lesions and relatively old age, suggested aEBVBLPD. Owing to the similarity in morphology, higher frequency at extranodal sites and poor prognosis, aEBVBLPD represents a differential diagnostic issue from classical Hodgkin's lymphoma when Reed-Sternberg cells are positive for EBV. [*J Clin Exp Hematopathol* 52(3) : 205-209, 2012]

Keywords: Hodgkin's lymphoma, aEBVBLPD, orbit, EBV, extranodal lymphoma

INTRODUCTION

Hodgkin's lymphoma (HL) typically originates at nodal sites and expands predominantly to neighboring lymph nodes. HL accounts for 10%-35% of head and neck lymphomas,¹⁻³ and Waldeyer's ring is the most common site of involvement.¹⁻⁵ However, as extranodal involvement of HL manifests clinically in less than 1% of cases,⁶ extranodal HL

of the head and neck that does not involve Waldeyer's ring is extremely rare.^{2,3,5}

Waldeyer's ring is a common Epstein-Barr virus (EBV) reservoir and EBV is associated with some forms of malignant lymphoma, including Burkitt's lymphoma, HL, non-Hodgkin's lymphoma and immunodeficiency-associated lymphoproliferative disorders (LPDs).⁷ Recently, Oyama *et al.* reported age-related EBV-associated B-cell LPD (aEBVBLPD), a new disease entity characterized by EBV-associated large B-cell lymphoma in elderly patients without predisposing immunodeficiency.⁸ This new disease entity is characterized pathologically by the appearance of Hodgkin (H)- and Reed-Sternberg (RS)-like giant cells,^{8,9} and age-related Epstein-Barr virus (EBV)-positive B-cell lymphoproliferative disorder (aEBVBLPD) showed an aggressive clinical course with a median survival of approximately 2 years.⁸ Therefore, the histopathological difference between aEBVBLPD and classical HL (cHL) has become an important diagnostic issue.

We herein describe a case of extranodal aEBVBLPD disorder limited to the intraorbital and maxillary sinus without prior systemic disease that was initially diagnosed as HL, and discuss the pathophysiology of this disease with reference to

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the literature.

CASE REPORT

A 59-year-old Japanese man visited our hospital complaining of pain in the orbit and maxilla in June 2008. Physical examination revealed swelling of the orbit and maxilla, but lymph node swelling and hepatosplenomegaly were not observed. Blood cell count and liver and renal function tests were normal, except for slight elevation of soluble interleukin-2 receptor (677 U/mL). Hepatitis C antibody was positive, but hepatitis B antigen, hepatitis B antibody, anti-human adult T-cell leukemia virus and anti-human immunodeficiency virus were negative. Computed tomography (not shown) and magnetic resonance imaging revealed lesions in the left orbit and maxilla (Fig. 1A & 1B), but lesions were not detected at other sites, including lymph nodes, spleen and liver. ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed accumulation of ¹⁸F-FDG in the left orbit and maxilla (Fig. 1C), but no other areas of disease were noted. Differential diagnosis between aEBVBLPD and HL was very difficult; therefore, through two biopsies, the patient was initially diagnosed as having HL, nodular sclerosis type, despite the CD20 positivity of H&RS-like giant cells. Bone marrow biopsy demonstrated no lymphoma cell infiltration, representing clinical stage IIA. We started combination chemotherapy consisting of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD). With four cycles of ABVD, followed by radiotherapy of the orbit at a dosage of 40 Gy, the patient showed complete response and maintained it for four years.

MATERIALS AND METHODS

Tissue specimens were fixed in formalin, routinely processed and then embedded in paraffin. For light microscopy, sections were stained with hematoxylin-eosin.

Immunocytochemistry was performed on paraffin sections using a Ventana automated stainer (BenchMark™) (Ventana, Tucson, AZ) according to the manufacturer's instructions.

A panel of antibodies against monoclonal human immunoglobulin light chains (κ and λ) (Novocastra, Newcastle, UK), IgM (Novocastra), leukocyte common antigen (LCA) (Ventana), CD3 (MBL, Nagoya, Japan), CD15 (Dako A/S, Glostrup, Denmark), CD20 (Nichirei Co., Tokyo, Japan), CD30 (Dako), latent membrane protein-1 (LMP-1) (Dako), EBV nuclear antigen-2 (EBNA-2) (Dako), CD79a (Roche, Basel, Switzerland), Oct-2 (Santa Cruz Biotechnology, Santa Cruz, CA) and BOB-1 (Santa Cruz Biotechnology) was used. For negative controls, normal mouse or rabbit serum was used in place of primary antibodies.

In situ hybridization (ISH) with EBV-encoded small RNA (EBER) oligonucleotides was performed to test for the presence of EBV small RNAs on formalin-fixed paraffin-embedded sections using a Ventana automated stainer (BenchMark™).

RESULTS

Biopsy specimens were obtained from the orbit and maxilla. On low-power examination, the lesion was characterized by fibrous tissue with necrosis and some areas showed nodule formation with an inflammatory background. On high-power examination, nodule areas, which were surrounded by fibrous tissue, contained a polymorphous population consisting of plasma cells, eosinophils, small lymphocytes and numerous histiocytes (Fig. 2A). In these areas, multi-nucleated H&RS-like giant cells were detected (Fig. 2A & 2B). Immunostaining demonstrated that the majority of H&RS-like giant cells expressed CD30 and CD15 (Fig. 2C & 2D), but 10% to 20% of H&RS-like giant cells expressed CD20 antigen (Fig. 2E). CD79a was negative in H&RS-like giant cells, while EBER was positive (Fig. 2F). Mature T-cells, with nuclear irregularities in some instances, and histiocytes

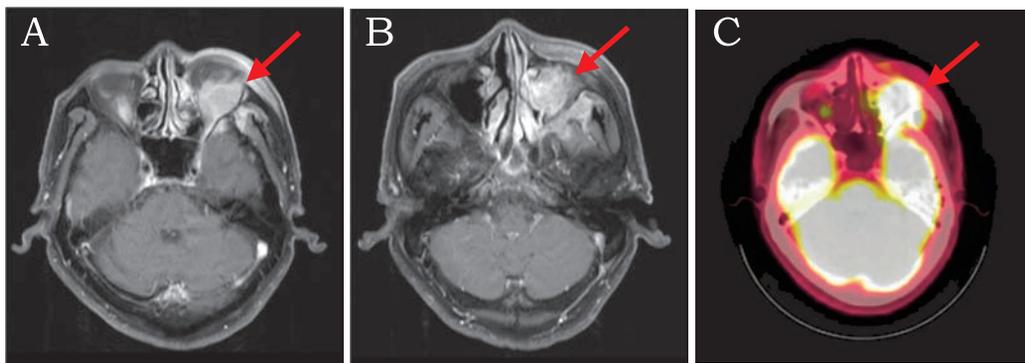


Fig. 1. (1A & 1B) Magnetic resonance imaging showing soft tissue mass in the left orbit and maxillary sinus before treatment. (1C) ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography showing accumulation of ¹⁸F-FDG in the left orbit and maxilla before treatment.

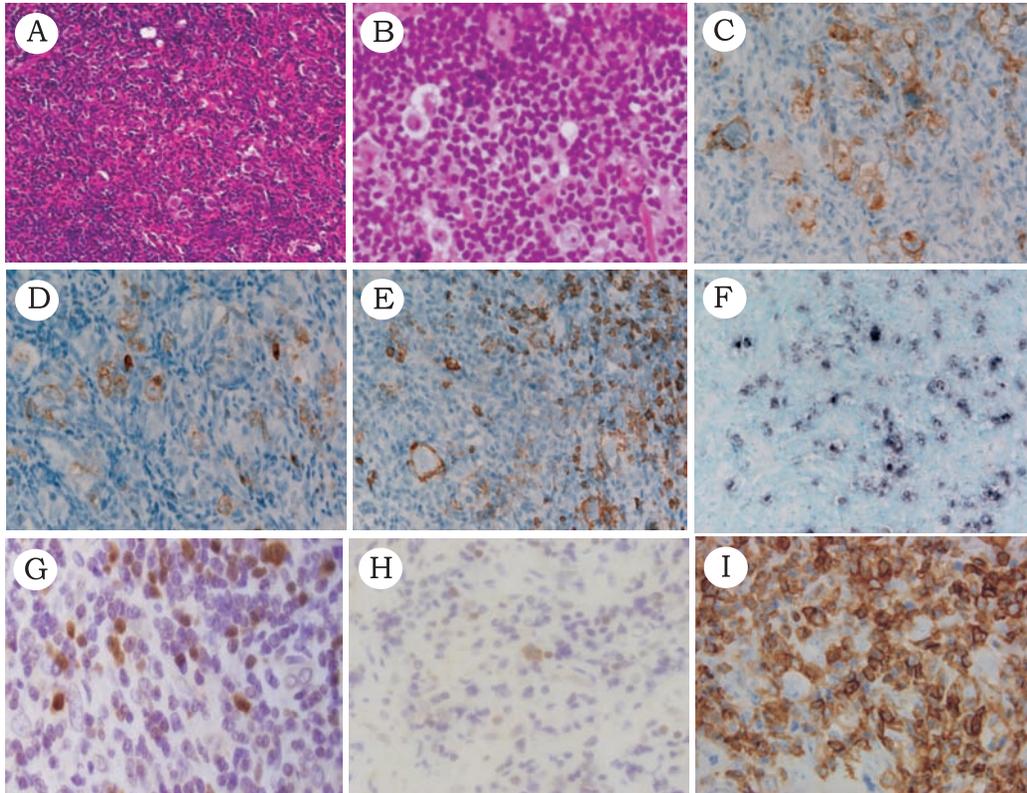


Fig. 2. Histological findings of biopsy specimen from maxilla. (2A & 2B) Fibrous tissues are observed. Multi-nucleated cells resembling Hodgkin- and Reed-Sternberg (H&RS)-like giant cells are present, and are surrounded by fibrous tissue with invasion of small lymphocytes. Histiocytes are predominant in the background. (2C-2I) Immunostaining and *in situ* hybridization of H&RS-like giant cells. The majority of H&RS-like giant cells were CD30⁺ (2C), CD15⁺ (2D), CD20⁺ (2E), Epstein-Barr virus-encoded small RNA⁺ (2F), BOB-1⁺ (2G), Oct-2⁺ (2H) and LCA⁺ (2I). (2A) HE stain, $\times 200$, (2B) HE stain, $\times 400$, (2C)-(2E) counterstained with methyl green, $\times 200$, (2F) counterstained with methyl green, $\times 400$, (2G)-(2I), counterstained with hematoxylin, $\times 400$.

were predominant in the background. Although CD20 was positive, these findings indicated cHL; however, further examination by immunostaining demonstrated that these H&RS-like giant cells were positive for Bob-1 (Fig. 2G), Oct-2 (Fig. 2H) and LMP-1 and a portion of large lymphoid cells expressed LCA (Fig. 2I), but were negative for EBNA-2. Even though EBNA-2 was negative in the H&RS-like giant cells, clinical features and immunostaining suggested polymorphous subtype aEBVBLPD.

DISCUSSION

The frequency of EBV-associated HL is reported to be as high as 40%,^{10,11} in which EBV DNA is typically detected in RS cells and/or mononuclear H cells. In head and neck lymphomas, while HL accounts for 10%-35% of all cases,¹⁻³ only 7 out of 354 cases of localized primary extranodal HL in this region have been reported.¹² Similarly, no cases of extranodal HL were reported in a series of 153 patients with head

and neck lymphomas.² To date, 23 cases with HL involving the oral cavity, oropharynx, nasopharynx, paranasal sinuses and larynx have been reported.¹³⁻²¹ Thus, the prevalence of extranodal HL in the head and neck region is very low, particularly involving the orbit and maxilla.

Recently, the WHO classification added a new disease entity called aEBVBLPD, which is characterized by EBV-associated large B-cell lymphoma in the elderly without predisposing immunodeficiency. This new disease entity is characterized pathologically by centroblasts, immunoblasts and H- and RS-like giant cells with varying degrees of reactive components. Approximately 70% of aEBVBLPD cases have been reported to occur at extranodal sites.^{8,9} Overall survival of aEBVBLPD was shown to be significantly inferior to that of diffuse large B cell lymphoma; its median survival time is 24 months.⁸ As this disorder has morphologic similarity to cHL, this variant represents a differential diagnostic issue from cHL. As the previously reported extranodal cHL cases in the orbit and maxilla have not been well investigated im-

munophenotypically, it is possible that some of the reported cases were aEBVBLPD.

Table 1 shows a comparison of the clinicopathological features between EBV⁺ cHL, aEBVBLPD polymorphous type and the present case (Table 1).²² While the immunophenotype of H&RS-like giant cells in aEBVBLPD is typically CD20⁺, CD10⁻, LMP-1⁺, EBNA2⁺, CD30⁺ and CD15⁻, RS cells in the present case were CD15⁺ and CD30⁺, which is similar to cHL. However, the CD20 positivity in the present case is not typical of cHL. Indeed, CD15⁻ is one of the characteristics of aEBVBLPD; however, CD15⁻ and CD30⁺ positive,²³ and CD20-negative²⁴ H&RS-like giant cells have been reported in LPDs associated with systemic rheumatoid diseases, particularly at extranodal sites.^{23,24} Dojcinov *et al.* reported that CD15 was positive in 43% of EBV⁺ mucocutaneous ulcer cases, including aEBVBLPD. They also suggested that caution is required when considering the presence or absence of CD15 as an independent determining factor for cHL or aEBVBLPD when the lesions involve extranodal sites.^{25,26} Furthermore, Bob-1 and Oct-2, which are thought to be B-lineage markers, were both expressed in the present case. Recent studies have rarely found the expression of Bob-1 in RS cells in cHL,²⁷ and the absence of functional Oct-2 and/or Bob-1 in RS cells in cHL has also been reported.^{28,29} In addition to immunophenotype, the characteristics of the present case, including the site of primary lesions, the absence of other lymph node lesions and the relatively old age, appear to suggest that the present case is aEBVBLPD, rather than cHL.

In the present case, CD15⁺ and CD30⁺ in H&RS-like giant cells were consistent with cHL, whereas the clinical features and the positive results for Bob-1, Oct-2, LCA and EBER in H&RS-like giant cells favor aEBVBLPD rather than cHL. Accordingly, the present case has features of both cHL and

large B-cell lymphoma. An aEBVBLPD may have a more aggressive clinical course and poorer outcome than EBV-negative DLBCL or EBV-positive cHL.^{8,9} In this respect, there is no consensus on the optimal treatment for this type of lymphoma. Although the patient in the present case received an HL-type regimen and attained CR, it is necessary to examine the treatment approaches further.

In conclusion, we report a rare extranodal EBV-positive LPD limited to the orbit and maxillary sinus without prior systemic disease. Owing to extranodal involvement and histopathological similarities, differentiation of aEBVBLPD from cHL is important. Accumulation of such cases and analysis of the immunophenotype is necessary to understand the pathophysiology.

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Table 1. Comparison of clinicopathological features

Clinical & pathological findings	EBV ⁺ cHL (> 50 years) (n = 108) (Shimoyama <i>et al.</i> ²²)	aEBVBLPD, polymorphous type (n = 34) (Shimoyama <i>et al.</i> ²²)	Present case
Age (median)	63	71	59
Sex M/F	83/25	20/14	M
Extranodal involvement > 1 site	17%	32%	Orbit, Maxilla
Immunophenotype			
CD20	19%	100%	Positive (10-20%)
CD15	60%	0%	Positive
CD30	93%	70%	Positive
EBER	100%	100%	Positive
LMP-1	87%	100%	Positive
EBNA-2	0%	25%	Negative
Median survival	Not reached	24 months	

EBV, Epstein-Barr virus; cHL, classical Hodgkin's lymphoma; aEBVBLPD, age-related Epstein-Barr virus (EBV)-positive B-cell lymphoproliferative disorder; M, male; F, female; EBER, EBV-encoded RNA; LMP-1, latent membrane protein-1; EBNA-2, EBV nuclear antigen-2

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