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Original Article

Epstein-Barr virus positive diffuse large B cell lymphoma of the elderly arising in nasal cavities and sinuses: a case report

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Abstract: Epstein-Barr virus-positive diffuse large B-cell lymphoma (EBV+DLBCL) of the elderly, characterized by a suboptimal response to therapy and poor survival rate, is a highly aggressive B-cell lymphoma without any known underlying immunosuppression or prior lymphoma. Unlike NK/T cell lymphoma, it rarely occurs in the nasal cavity. Here we report a case of EBV+DLBCL of the elderly primarily arising in the nasal cavities and sinuses in a 62-year-old female who presented with nasal congestion and left eye blindness. CT scan showed that the neoplasm invaded bilateral nasal cavities and adjacent sinuses, and bilateral eye sockets. Microscopically it showed diffuse infiltration of medium to large lymphocytes with extensive necrosis. The atypical cells were positive for CD20, MUM1, and CD30, negative for CD10, CD15, CD2, CD3, TIA1, CD21, and CD56. In situ hybridization for Epstein-Barr virus-encoded ribonucleic acid was positive. The patient underwent 5 cycles of CHOP regimens, and partial remission was achieved, but the patient died from infection and multiple organ failures. It was only 5 months from the time of diagnosis to the patient demise.

Keywords: Epstein-Barr virus, diffuse large B-cell lymphoma, elderly, nasal cavities and sinuses

Introduction

Epstein-Barr virus-positive diffuse large B cell lymphoma (EBV+DLBCL) of the elderly is considered to be a new lymphoproliferative disorder and classified as a new provisional entity in the 4th edition of the World Health Organization (WHO) Classification of tumors of hematopoietic and lymphoid tissues [1]. It is defined as an EBV positive monoclonal large B-cell proliferation that occurs in patients older than 50 years with no known immunodeficiency or history of lymphoma [2]. It shows similarities in many respects to immunodeficiency associated lymphoproliferative disorder (LPD) and is believed to be related to immunological deterioration as a result of the aging [3]. Histologically, it is characterized by complete effacement of normal nodal architecture by atypical large B cells including immunoblasts and Hodgkin/Reed-Sternberg-like cells accompanied with variable amounts of inflammatory cells in the background [4].

EBV+DLBCL of the elderly shows an aggressive clinical course with a median survival of approximately 24 months [5]. More than half of the cases have advanced disease with poor prognostic International Prognostic Index (IPI) scores at the time of diagnose [6]. The disease tends to be activated B cell like (ABC) rather than germinal center B-cell-like (GCB) immunophenotype. Approximately 70% of the patients present with extra nodal involvement, such as the stomach, ileum, testis, tonsil, and skin [7]. To our knowledge, it is extremely rare arising in the nasal cavity. We herein report a rare case of EBV+DLBCL of the elderly arising in the nasal cavities and sinuses and discuss the clinicopathological characters of the disease.

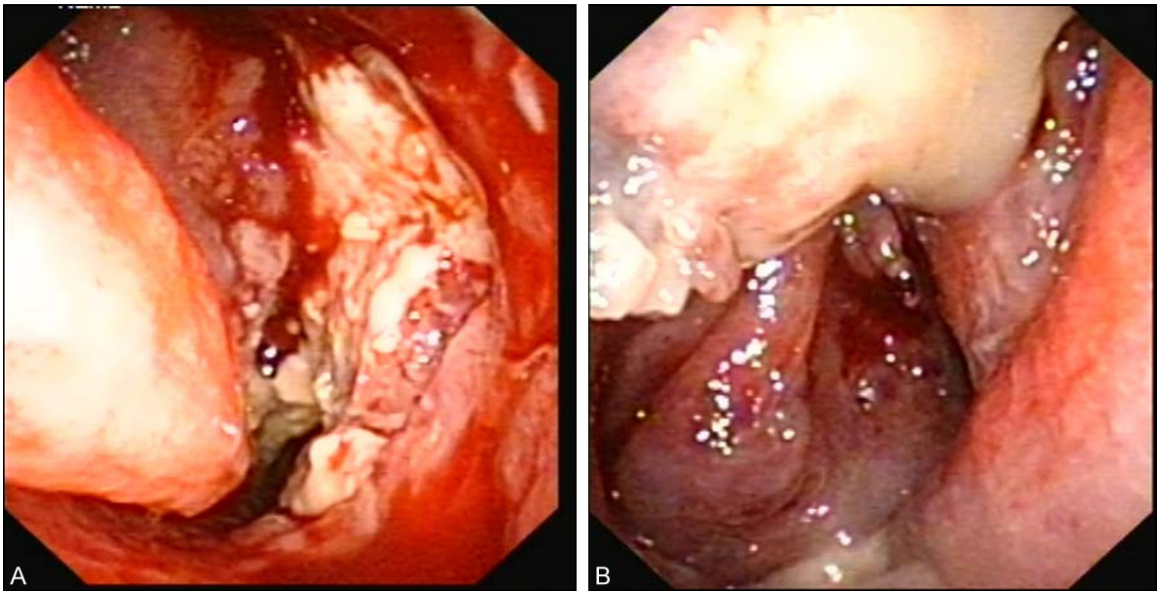

Figure 1. Nasal endoscopy examination revealed bilateral uneven neoplasm, inferior turbinate hypertrophy, and nasal septum adhesion. A. Right nasal cavity. B. Left nasal cavity.

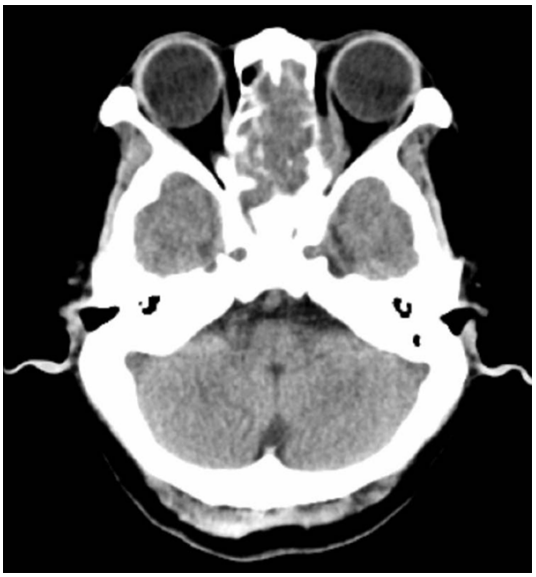

Figure 2. Nasal sinus CT showed the invasion of ethmoid sinus and left eye socket.

Case report

A 62-year-old Chinese female visited our hospital complaining of continuous nasal congestion for six months and left eye blindness with headache for ten days. There was no fever, weight loss, night sweat and any other neurological sign. Physical examination showed no superficial lymphoadenopathy and hepatosplenomegly. Nasal endoscopy examination revealed the entire bilateral nasal cavities were filled with white and gray soft tissues, brittle and prone to bleeding (**Figure 1A**, **1B**). Nasal sinus CT showed that the entire bilateral nasal cavities were filled with soft tissues which extended into the ethmoid sinus, front sinus, sphenoid sinus, and the left eye socket (**Figure 2**).

Histological examination showed diffuse infiltration with medium to large lymphocytes accompanied by extensive necrosis. Tumor cells were pleomorphic, many large transformed cells/immunoblasts were frequently observed, with rich eosinophilic cytoplasm, irregular nuclei and multiple distinct nucleoli. These large atypical cells were positive for CD20, MUM1 and CD30, negative for CD10, CD15, CD2, CD3, TIA1, CD21 and CD56, and in situ hybridization for Epstein-Barr virus-encoded ribonucleic acid was positive, the background scattered small lymphocytes were CD3/TIA1 positive and the residual epithelial cells were AE1/AE3 positive (**Figure 3A-I**).

Further examination such as thoracic and abdominal CT examination, bone marrow biopsy did not showed more tumor invasion in other sites. The dehydrogenase (LDH) level was normal and the ECOG score of performance Status was 0. Review of clinical data and patient history did not disclose any known immunodefi-

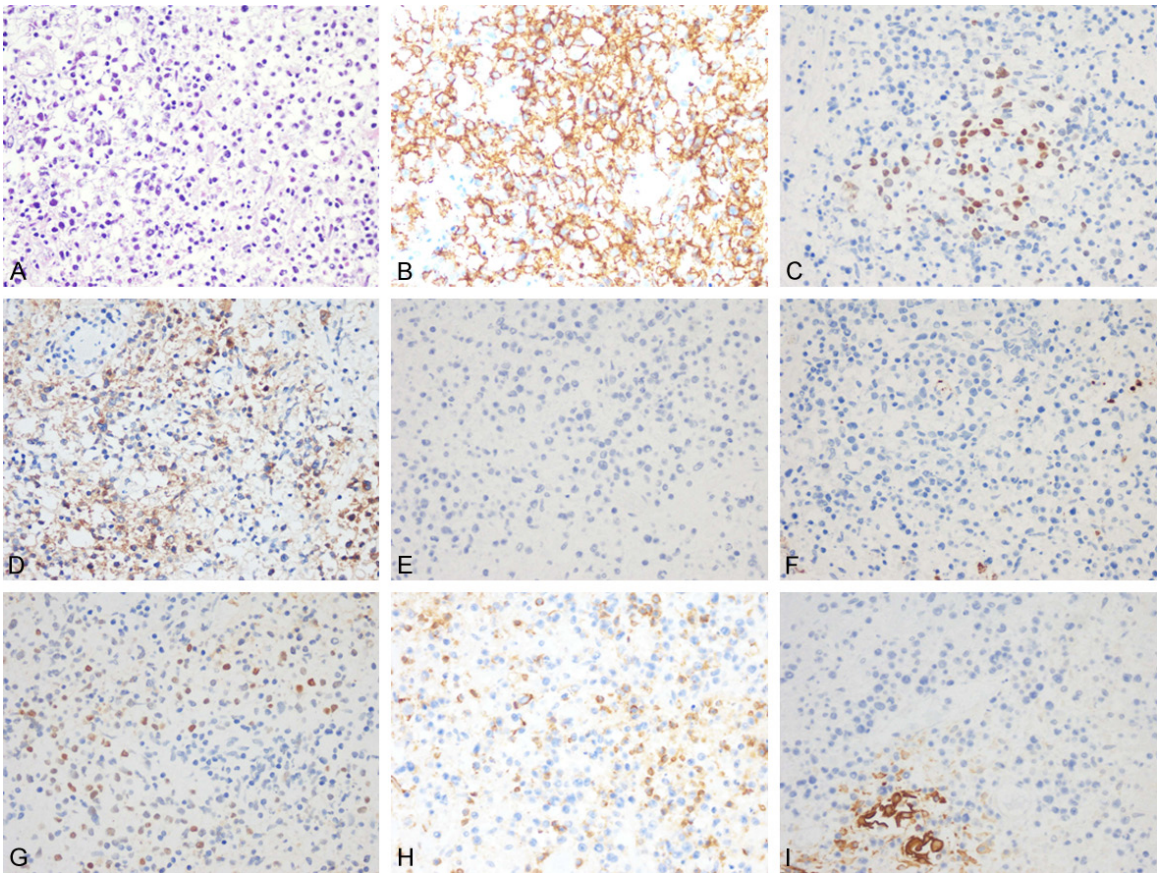

Figure 3. Histological immunohistochemical feature and Epstein-Barr virus encoded RNA (EBER) of the surgical specimen (200×). A. Histological examination shows diffuse infiltration with medium to large lymphocytes accompanied by geographical necrosis. B. Neoplastic cells are strongly positive for CD20, consistent with a B-cell lineage. C. Neoplastic cells are positive for MUM-1, consistent with non-germinal center cell phenotype. D. Neoplastic cells are positive for CD30. E. Neoplastic cells are negative for CD10. F. Neoplastic cells are negative for CD15. G. The nuclei of neoplastic cells are positive for EBER in-situ hybridization. H. The small lymphocytes in the background are positive for T-cell marker CD3. I. The residual epithelial cells are positive for AE1/AE.

ciency disease such as AIDS and the hematopoietic or lymphoid tumors. So the patients were diagnosed as age-related EBV+DLBCL of the elderly, stage II AE, with an IPI score of 2. The patient underwent 5 cycles of CHOP chemotherapy. After the second course, nasal congestion, headache symptoms were disappeared and visual acuity was improved. After the fourth course of treatment, CT scan showed partial remission. But after the fifth course, the patient developed intestinal infection, multiple organ failure and death. It was only 5 months from the time of diagnosis.

Discussion

EBV+DLBCL of the elderly is a distinct subtype of DLBCL first described by Oyama in 2003 [8]. As the name suggests, it has a predilection for the elderly with a median age of 71 years (age range: 45-92 years), and 20-25% of the patients are older than 90 years of age [1]. The prevalence of EBV+DLBCL of the elderly in Asians has been reported to be 8.7-11.4%, in contrast of less than 5% in western populations [2].

EBV infection is the crucial risk of EBV+DLBCL of the elderly [3]. It has been shown that the EBV encoded latent membrane protein 1 gene (LMP-1) is responsible for up regulating cell adhesion molecules and activating multiple cell signal pathways [9]. It promotes cell immortality by up regulate of anti-apoptotic proteins such as Bcl-2, MCL-1 and A20, hence EBV is able to drive B-cell proliferations [10]. EBV+DLBCL of the elderly has similar clinical and histological features as other EBV+B-LPDs, in which the pathogenesis is associated with T-cell function

decrease due to the patients' reduced immune function, but there is no known predisposing immunodeficiency history such as transplantation or lymphoma. As we know the incidence of EBV infection is gradually increased with age [11]. It has been proposed that EBV+DLBCL of the elderly may be related to an immunologic deteriation intrinsic to the aging process [12]. such as thymic atrophy, reduced output of new T lymphocytes and deficiencies in the cytokine production [13].

The clinical features of EBV+DLBCL of the elderly are variable, may include lymphadenopathy, B-symptoms, etc. Extranodal sites involvement is documented in up to 70% of patients, the most common sites are the skin, lung, tonsil and stomach, rarely in nasal cavity. Other clinical manifestation such as elevated LDH, a high IPIs, and a high stage are also common [4].

Histologically, based on the ratio of malignant cells to inflammatory cells, EBV+DLBC of the elderly were divided morphologically into large-cell lymphoma and polymorphous subtypes, the former is characterized by having areas where large lymphoid cells with relatively notable monomorphic dominant appearance, and the polymorphous subtype is characterized by the scattered distribution of large cells with polymorphous composition. But there was no significant clinical difference between these two groups [5]. Typically the neoplastic cells show expression of pan B-cell markers, specifically CD20 and/or CD79a and PAX-5, EBV-encoded RNA (EBER) in situ hybridization is positive, CD30 is variably positive and CD15 is negative that should be used to distinguish from classic Hodgkin lymphoma (cHL).

In our patient, the neoplasm cells are polymorphic, accompanied by extensive necrosis and small lymphocyte in the background. IHC showed CD20 positive, EBER ISH positive, T cells and NK cells markers were negative, consistent with the polymorphous subtype, CD10 negative, and MUM1 positive that falls in a post-GC phenotype.

Currently, there is no uniformly accepted treatment for EBV-positive DLBCL of the elderly other than the current standard therapy for DLBCL. The combination of cyclophosphamide, adriamycin, vincristine and prednisone (CHOP) was the most common regimen. Due to CD20 positivity, rituximab can be added to chemotherapy. Unfortunately, the treatment response is usually poor and the outcome is worse than the EBV-negative DLBCL patients [2, 14]. High dose chemotherapy with stem cells transplant may improve the outcome, and is now under investigation [14, 15]. Given that the EBV-positive DLBCL of the elderly is an aggressive post germinal center B-cell neoplasm characterized by prominent NF-κB activation [16], targeting the NF-κB pathway could constitute a rational therapeutic approach, however further studies are required.

Our patient was treated with CHOP regimen, rituximab was not used for the personal reason. Although she was not older than 70 and without B symptoms, those are two independent predictors of poor outcome [5], the response to chemotherapy was suboptimal. Her symptoms were improved after 2 courses of treatment, but the patient has not yet reached CR after 4 courses and was died from gastrointestinal infection.

Conclusion

The patient demonstrated a progressive disease course and was less responsive to standard chemotherapy. More studies are needed to improve the treatment and prognosis of this rare and devastating disease.

Disclosure of conflict of interest

None.

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