Review Article

Senile Epstein-Barr Virus-Associated B-Cell Lymphoproliferative Disorders : a Mini Review

Yoshie Shimoyama[1], Takashi Oyama[2], Naoko Asano[3], Aya Oshiro[3], Ritsuro Suzuki[4],

Yoshitoyo Kagami[5], Yasuo Morishima[5] and Shigeo Nakamura[1]

Epstein-Barr virus (EBV) is associated with a number of malignant lymphomas, including Burkitt lymphomas, Hodgkin lymphomas (HLS), immunodeficiency-associated lymphoproliferative disorders (LPDs), and subset of diffuse large B-cell lymphomas. We have recently identified a series of elderly patients afflicted with EBV-associated (EBV-positive) B-cell LPDs in the absence of predisposing immunodeficiencies ; we have named these neoplasms "senile" EBV+ B-cell LPDs. The large series of patients with this disease (n=76) provided additional evidence that this neoplasia, with a median age of onset of 71 years, has the highest incidence in elderly patients aged ＞ 50 years, suggesting that this disease may be related to the immunological deterioration that occurs during the aging process. These lesions were pathologically characterized by varying numbers of Hodgkin and Reed-Sternberg (HRS)-like giant cells, often posing a diagnostic problem differentiating this condition from HL. Recent studies, however, have indicated that HL and non-Hodgkin lymphoma (NHL) may be more closely related than previously implied, promoting the general consensus that HRS cells are derived from B cells in most HL cases. The relationship between EBV+ HL and EBV+ B-cell LPDs remains to be clarified. This review provides a unique opportunity to highlight the gray areas between EBV+ HL and EBV+ B-cell LPDs. Further investigations are necessary to clarify the interrelationship, including their overlapping morphological and biological features.

Key words Epstein-Barr virus, B-cell lymphoma, Hodgkin lymphoma, immunodeficiency, senescence, aging

INTRODUCTION

In the past few decades, human malignancies associated with Epstein-Barr virus (EBV), including a variety of malignant lymphomas and carcinomas, have been well documented ; our knowledge of these diseases is now greatly expanded. As the epidemiology of EBV-associated (EBV-positive) human diseases is quite complex, the true contribution of EBV to the pathogenesis of these diseases remains to be elucidated.

According to the World Health Organization (WHO) classification of lymphoid tumors[1,2], disease entities, such as endemic Burkitt lymphoma, lymphomatoid granulomatosis, and extranodal NK/T-cell lymphoma of nasal type, reveal a high prevalence of EBV positivity. This virus is also clearly involved in the pathogenesis of the majority of B-cell lymphomas arising in patients with iatrogenic or congenital immunosuppression. The association of EBV is heterogeneous in conventional diffuse large B cell lymphomas (DLBCL), peripheral T cell lymphomas, and Hodgkin lymphomas (HL). The clinicopathologic significance of EBV in these diseases remains to be clarified. We recently have documented 22 cases of senile EBV-associated B cell lymphoproliferative disorder (B cell LPD), arising in elderly patients aged older than 60 years in the absence of predisposing immunodeficiencies[3]. The recognition of this disease has prompted us to analyze further its clinicopathologic profile and reconsider its relationship with EBV+ HL.

SENILE EPSTEIN-BARR VIRUS-ASSOCIATED B-CELL LYMPHOPROLIFERATIVE DISORDERS

In 2003, Oyama *et al*. reported 22 cases of EBV-associated (EBV-positive) B cell LPDs in patients without any predisposing immunodeficiencies[3]. All of these patients were over 60 years of age, with a median age of 76 years. This condition was accompanied by extranodal involvement in 18 cases (82%). Biopsied specimens contained varying numbers of centroblasts, immunoblasts, and Hodgkin and Reed-Sternberg (HRS)-like giant cells. Necrosis and an angiocentric pattern were also frequently seen. The cases

were divided into two groups based on the morphology of the malignancy. Thirteen cases were of the polymorphic subtype, showing a polymorphous composition and inflammatory background. Nine patients had a large-cell lymphoma subtype with diffuse proliferation of large lymphoid cells, although the patients constituted a continuous spectrum of pathology. The tumor cells typically expressed CD20 and/or CD79a ; *in situ* hybridization revealed an association with EBV. LMP1 was detected in all of the cases, while EBNA2 was seen in seven cases (32%), indicating latency II and III status, respectively. Eight of the 18 patients who received chemotherapy with a CHOP regimen showed an aggressive disease progression within a year of diagnosis. Although the clinicopathologic profile of this series was analogous to that seen in immunodeficiency-associated B cell LPDs, none of the patients showed any evidence of underlying immunodeficiencies. This disease may be related to an immunological deterioration or senescence in the immune system resulting from the aging process in these patients. Therefore, this group has been denominated as senile or age-related EBV-associated B cell LPD.

We extended our analysis to include 76 cases of this unique disorder, the clinicopathologic picture of which conformed to that previously described (Table 1). Briefly, there were 39 male and 37 female patients, with ages ranging from 50 to 92 years old and a median age of 71 years. According to the definition of the disease, all patients were negative for anti-human immunodeficiency virus antibodies and did not have any of the clinical symptoms that would suggest immunodeficiency. Specimens were obtained from lymph nodes in 43 patients, the stomach in seven cases, Waldeyer's your's ring in six patients, the skin in five individuals, the lung in four cases, the nasal cavity in four patients, and other sites in seven individuals. Morphologically, the patients were subdivided into 31 cases with polymorphic subtype disease and 45 cases with large cell lymphoma (LCL) subtype disease with supportive data of CD20 and/or CD79a positivity to distinguish these conditions. EBV association was seen for all tumor cells (Table 2). Notably, senile or age-related B cell LPDs have a tendency to become more common with an increasing age, and characteristically demonstrate frequent extranodal involvement. The detailed clinicopathologic characteristics of these diseases are currently under investigation, but have preliminarily provided additional data, including the significant difference in prognosis between patients with polymorphic and LCL subtypes (median survivals of 40 vs. 9

months, respectively, *P*=0. 04).

HODGKIN AND REED-STERNBERG-LIKE CELLS IN EBV-ASSOCIATED B-CELL LYMPHOMAS

In the large series of senile EBV[+] B cell LPDs, histological assessment revealed a varying number of HRS-like giant cells frequently exhibiting expression of CD30, which pose a serious diagnostic problem differentiating this condition from EBV-positive classical Hodgkin lymphoma (CHL). In a subset of patients with the LCL subtype of senile EBV[+] B cell LPD, the number of HRS-like giant cells was paradoxically greater than that seen in CHL. In the past, these EBV-positive B cell LPDs may have been confused with CHL due to the lack of clear-cut diagnostic criteria. As the differential diagnosis is sometimes impossible to resolve by histologic examination alone, the key to distinguishing between these EBV[+] B cell LPDs and EBV[+] HL now depends on recognition of the degree of expression of B cell markers, such as CD20 and CD79a, on the tumor cells. EBV[+] B cell LPD is always characterized by the expression of CD20 and CD79a and is associated with light chain restriction in many of large cells. The issue remains, however, that CD20 positivity is found in approximately 10- 20% of HL cases in a small population of HRS cells.

Accumulating molecular biological evidence has elegantly revealed that HRS cells are predominantly derived from lymphocytes of the B cell lineage in many or most of CHL cases[4,5]. As the range of histologic appearances of both EBV[+] CHL and senile EBV[+] B-cell LPD is so wide, it is not surprising that distinguishing between these two diseases may be difficult or impossible in a subset of cases.

Table 2. Senile EBV-associated B cell lymphoproliferative disorders : Pathology (n=76)

- Often polymorphic composition
- Necrosis, histiocytes, and other reactive components
- Angiocentric growth pattern
- Reed-Sternberg-like giant cells
- Polymorphous subtype (n=31)
- Large-cell lymphoma subtype (n=45)

Table 1. Senile EBV-associated B cell lymphoproliferative disorders : Clinical manifestations (n=76)

- M : F=39 : 37
- Age range from 50 to 92 years old, median 71
- No evidence of underlying immunodeficiency
- Lymph node 43 cases, stomach 7, Waldeyer's ring 6, skin 5, lung 4, nasal cavity 4, oral cavity 2, spleen 2, vagina 1, spine 1, and pancreas 1

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EBV-ASSOCIATED CLASSICAL HODGKIN LYM- PHOMA AND EBV-ASSOCIATED B-CELL LYM- PHOMAS

Recent epidemiological studies[3] shed light on the distinctive features of EBV-positive CHL, implying that EBV-associated and non-associated cases may represent two distinct etiological entities. This implies that the biologic properties, such as an EBV association, may precede morphological evaluation to further our understanding of the allover clinicopathologic profiles of HL. Biological interfaces or overlaps between CHL and diverse subtypes of B cell lymphomas may therefore exist.

The clinicopathologic significance of EBV as a prognostic marker in HL patients remains controversial. Studies by Clarke et al.[6] and Stark et al.[7] demonstrated that EBV positivity of HRS cells correlated with significantly poorer survival in HL patients aged 45-79 years of age or aged 60 years and over, respectively. Starke et al.[7] also determined that EBV status had an adverse effect on clinical outcomes especially in elderly patients (70 years of age and above) compared with that in a younger elderly group (60-69 years of age). Enblad et al.[8] also reported that EBV-positive CHL patients were more likely to be older, have increased B symptoms, and more advanced disease. These patients also exhibited a reduced survival in comparison to EBV-negative patients[8]. Recently, Ganhdi et al.[3] and Jarrett et al.[9-11] indicated that the decline in EBV-specific cellular immunity that occurs with age may contribute to the development of EBV-positive CHL in older patients. These conclusions also reinforce the recognition of senile EBV[+] B cell LPDs as a continuous spectrum of EBV[+] CHL.

CONCLUSIONS

Recent observations have indicated that HL and non-Hodgkin's lymphoma (NHL) may be more closely related than previously believed, with the achievement of a general consensus of the B cell derivation of HRS cells in most HL cases[12-14]. As the prototypic cytomorphology of HRS cells is shared by transformed large B lymphocytes, especially those harboring EBV, a biologic overlap between HL and NHL does exist. It is tempting to speculate that EBV-positive CHL and EBV-positive B-cell LPD may constitute a continuous spectrum of disease[15]. Further studies, however, are required to understand in detail the clinicopathologic profiles, the immunology, the molecular biology, and the therapeutic strategies for treatment of these diseases.

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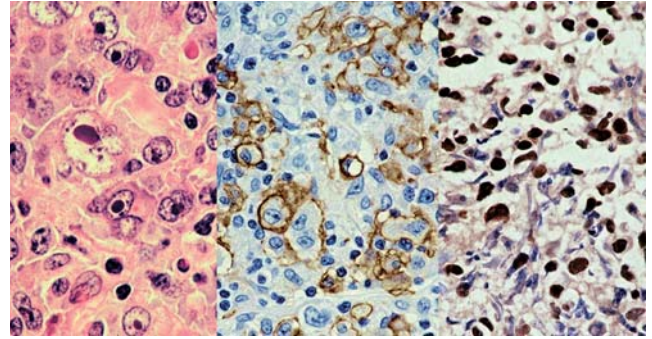
Fig. 1. Senile Epstein-Barr virus (EBV)-associated B cell lymphoproliferative disorder of the large cell lymphoma subtype arising in a 62-year-old male. The lesion reveals Hodgkin and Reed-Sternberg-like giant cells (Fig. 1a, left) that are positive for CD20 (Fig. 1b, middle) and EBER by *in situ* hybridization (Fig. 1c, right).

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