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Case Report

Histiocytoid Epstein-Barr virus-positive follicular lymphoma with large B transformation: a case report and review of literature

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Abstract: Epstein-Barr virus-positive follicular lymphoma (EBV-positive FL) is extremely uncommon, especially a histiocytoid morphology. Here we present a 70-year-old man who had EBV-positive FL with diffuse large B-cell lymphoma (DLBCL) transformation in the left cervical lymph nodes.

Keywords: Epstein-Barr virus, follicular lymphoma, diffuse large B-cell lymphoma, histiocytoid morphology

Introduction

Epstein-Barr virus (EBV) is a gamma herpesvirus that persistently infects more than 90% of adults worldwide. EBV infection primarily targets B cells and epithelial cells and EBV is commonly associated with several lymphomas including Hodgkin lymphomas, Burkitt lymphoma, and some subtypes of diffuse large B cell lymphoma (DLBCL). EBV-positive FL is extremely rare and there are only nine English papers [1, 3-7, 11-13] in PubMed at present. To our knowledge, this is the first detailed report to describing a case of histiocytoid EBV-positive FL with large B transformation.

Case report

A 70-year-old man was admitted to the hospital with a rapidly growing painless mass on the left neck. Twenty days prior, an irregular mass was unexpectedly found on the left side of his neck and grew rapidly after hot compression physical therapy. By physical examination, a hard irregular mass of about 6×5 cm could be palpated on the left side of the neck with a smooth surface. Patient had no B symptoms. Laboratory tests showed LDH 265 u/L and blood EBV nucleic acid was negative. No obvious abnormality was found in hemogram indexes. PET CT showed multiple enlarged lymph nodes in bilateral parotid glands, neck and supraclavicular fossa, mediastinum, hilum of lung, pelvic cavity, retroperitoneum and left inguinal region, SUVmax was about 14-20, spleen was large and metabolism was high. The patient had needle biopsy without a definite pathologic diagnosis and then underwent surgical resection of two lymph nodes from the left neck. The specimen received in formalin consisted of two lymph nodes with a maximum diameter distribution of approximately 1.5 cm and 0.6 cm. The cut surface was gray white and tough. Under low magnification, most of the tumor tissues in the lymph nodes presented diffuse infiltration, but the tumor tissue in the lymph node with a diameter of 0.6 cm showed nodular growth (**Figure 1A**), Under high magnification, tumor cells had histiocytoid morphology with abundant and pink cytoplasm, irregular nuclei, obvious nucleolus and mitosis (**Figure 1B**), and some cells were spindle-shaped. Immunohistochemistry showed that most of the tumor tissues were diffusely and strongly positive for CD20, BCL6 and BCL2. CD21 showed that most of FDC network disappeared and the Ki-67 proliferation rate was approximately 70-80%.

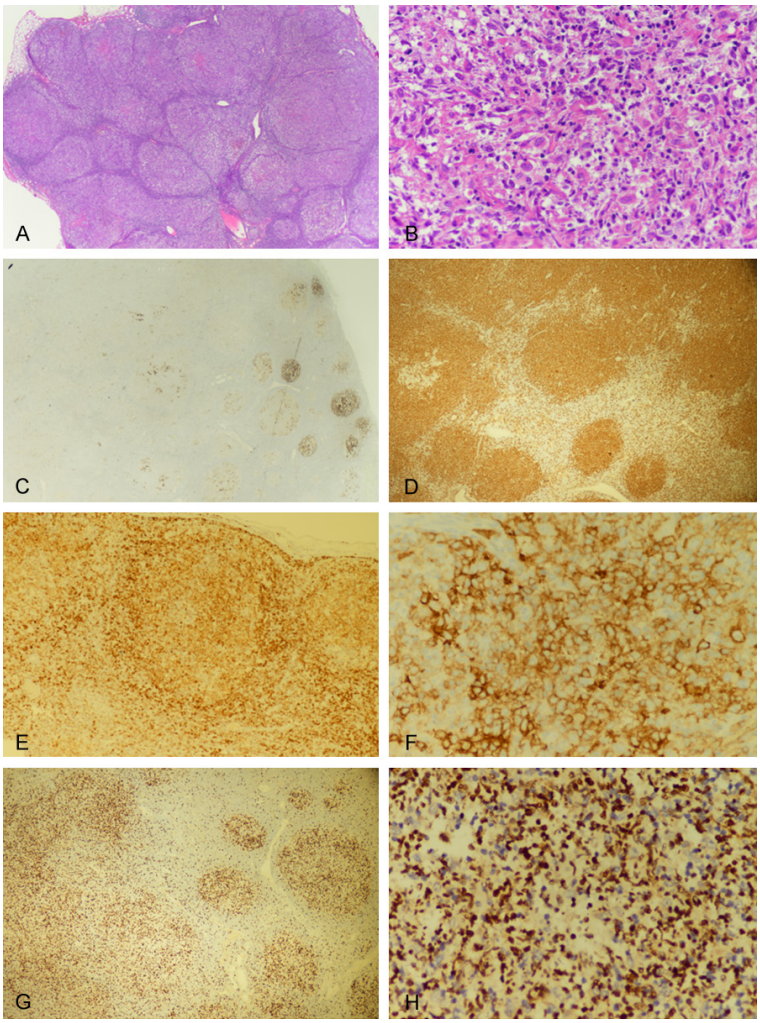

Figure 1. H&E and IHC of EBV-positive FL with DLBCL transformation. A. The tumor tissue in the lymph node with a diameter of 0.6 cm showed nodular growth (H&E ×20). B. Tumor cells had histiocytoid morphology and had abundant and pink-stained cytoplasm, irregular nuclei with obvious nucleolus and mitosis (H&E ×400). C. CD21 showed most of the FDC networks in the node were destroyed and disappeared, but a few FDC networks were found at the edge of the lymph node (IHC ×20). D. CD20 was positive in the follicular and diffuse areas (IHC ×40). E. The presence of BCL2 in germinal centers proved the presence of follicular lymphoma (IHC ×100). F. CD30 was positive in most tumor cells (IHC ×400). G. The indexes of Ki67 were about 70-80% (IHC ×40). H. In situ hybridization EBER was positive at the rate of about 100/HPF (IHC ×400).

In the 0.6 cm lymph node with nodular growth, CD21 staining confirmed that most of the FDC networks in the node were destroyed and disappeared. A small number of FDC networks was found at the edge of the lymph node, and the FDC network was filled with histiocytoid tumor cells, which were positive for CD20, BCL6, and BCL2. The index of Ki67 was about 70-80% and the in situ hybridization EBER was about 100/HPF (**Figure 1C-H**). Due to the presence of this part of FL, the final pathological diagnosis was high-grade EBV-positive FL with DLBCL transformation: 1. EBV-positive DLBCL (90%), 2. high-grade EBV-positive FL (10%). The patient received chemotherapy with R-CHOP regimen.

Discussion

EBV-related lymphomas mostly originate from B-cell lines, but only a few are from NK/T cells [8]. In the 2016 revision of the WHO classification of lymphoid neoplasms, EBV-related large B-cell lymphomas include: EBV-positive DLBCL, NOS, EBV-positive mucocutaneous ulcer (EBVMUC), DLBCL associated with chronic inflammation, lymphomatoid granulomatosis (LYG), plasmablastic lymphoma (PBL), primary effusion lymphoma (PEL), and HHV8-positive germinotropic lymphoproliferative disorder (GLPD) [8, 9].

FL is the most common indolent and second most common non-Hodgkin lymphoma subtype. It is a neoplasm derived from follicle center B cells, typically composed of centrocytes and centroblasts, in variable proportions according to the lymphoma grading [10]. EBV-positive FL is an uncommon disease and occurs with a prevalence of about 2.5% of FL [1, 6, 7]. The first report in 2011 [4] described the case of a 65-year-old woman who had simultaneous occurrence of FL, Kaposi sarcoma (KS), and Castleman's disease (CD) with coinfection by HHV-8 and EBV. The FL component of the tumor was grade 3A and EBER1-positive. Menon et al. [3] in 2013 reported a 53-year-old white woman was diagnosed as follicular lymphoma (grade 1 to 2) that was EBV negative. But after one year of treatment, the patient progressed to follicular grade 3 with classic Reed-Sternberg (RS)

and Hodgkin cells-like morphology. EBER was positive in Hodgkin-like cells and a few background cells in the neoplastic follicles. Van der Horst et al. [11] in 2015 described a 50-year-old male with EBV-positive primary cutaneous follicular center lymphoma, who subsequently developed an EBV-positive DLBCL after completing radiotherapy. Orlandi et al. [12] and Granai et al. [13] also described cases of EBV-positive DLBCL evolved from a previous FL after treatment. Kurt et al. in 2018 [1] reported a clear case of follicular lymphoma grade 3A with EBER positive. Mackrides et al. [6, 7] found EBV-positive FL was rare and occurred with a prevalence rate of 2.6% in an unselected cohort of 382 FL patients and 2.5% in 488 patients; and the EBER-positive rate was more common in high-grade FL. EBV-positive FL trended towards more aggressive features than EBV-negative FL and shared some clinicopathologic features with EBV-positive DLBCL, such as frequent strong CD30 expression and diffuse EBER positivity (generally >75% of lymphoma cells). Because of the incidence of EBV in high-grade FL, it is suggested to be screened for EBER in all high-grade cases.

Following the treatment principle of FL [14, 15]: For patients with asymptomatic, low tumor burden, low-grade FL, the watch-and-wait approach is generally implemented until the occurrence of symptoms or signs of advancing lymphoma (e.g., B symptoms, organ involvement, ascites or pleural effusion, rapid progression, or bone marrow infiltration). For patients with advanced disease, R-CHOP (rituximab added to cyclophosphamide, doxorubicin, vincristine, and prednisone) is recommended with other chemotherapy drugs (such as ibuprofen, lenalidomide) or not. Because of the low incidence and the current limited number of reported cases, it is difficult to draw definite conclusions about lymphoma genesis or transformation and prognosis of EBV-positive FL. In the future, larger cohorts will be needed to definitively assess the impact of EBV on prognosis and clinical management of EBV-positive FL.

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The case report and any accompanying report pictures were signed with informed consent from the patient's family members.

Disclosure of conflict of interest

None.

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