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Teaching cases

A malignant lymphoma with histological features and immunophenotypic profile intermediate between EBV-positive diffuse large B-cell lymphoma and EBV-positive classical Hodgkin lymphoma in a 67-year-old female: A "gray zone" lymphoma associated with Epstein-Barr virus in the elderly

Endi Wang*, Paulie Papavassiliou, Siby Sebastian

Department of Pathology, Duke University Medical Center, Durham, NC, United States

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ABSTRACT

Epstein–Barr virus (EBV) can be associated with both classical Hodgkin lymphoma (cHL) and non-Hodgkin lymphoma of the B-cell type, particularly in immunodeficient patients or elderly individuals. While polymorphic variants of EBV-positive large B-cell lymphoma (EBV+ DLBCL) frequently resemble cHL in morphology, and thereby may cause diagnostic difficulty, a true gray zone lymphoma with overlapping morphological and immunophenotypical features of EBV+ DLBCL and EBV+ cHL has not been reported in the literature. We describe a unique case of an EBV+ malignant lymphoma of B-cell origin with hybrid features of EBV+ DLBCL and EBV+ cHL in a 67-year-old female without an identifiable etiology for immunodeficiency. The biopsy of an enlarged lymph node showed a polymorphic infiltrate containing Reed–Sternberg-like pleomorphic large cells, which were positive for CD30 and CD15. Although CD20 was negative and PAX5 and CD45 were down-regulated, the pleomorphic large cells expressed multiple other B-cell antigens which are characteristically absent in cHL. EBV-encoded RNA hybridization (EBER) studies demonstrated nuclear reactivity in the large cells as well as in the smaller bystander cells. A clonal rearrangement of the immunoglobulin heavy chain gene was also detected by PCR. Although the results of the EBV and genotypic studies suggest this case may be an example of EBV+ DLBCL of the elderly instead of EBV+ cHL, the immunophenotype is strikingly ambiguous. Thus, this case may represent an interface between EBV+ DLBCL and EBV+ cHL.

Introduction

Epstein–Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL) of the elderly is an age-related clonal B-cell neoplasm in association with EBV infection [10–12,16]. While this occurs in patients >50 year old without any known immunodeficiency or an identifiable etiology which can induce immunodeficiency, it shares many features with congenital, iatrogenic or other acquired immunodeficiency-associated B-cell lymphoproliferative disorders in clinical presentation and histopathology [11,16]. For instance, EBV+ DLBCL of the elderly has a propensity to involve extranodal sites and has a broad morphologic spectrum ranging from polymorphic lymphoproliferative disorder to overt large cell lymphoma [10,11,16]. As seen in other immunodeficiency-associated B-cell lymphoproliferative disorders, a polymorphic subtype of EBV+ DLBCL of the elderly may resemble classical Hodgkin lymphoma (cHL) by having scattered Reed–Sternberg (RS) cells, or their variants, in a background of mixed inflammatory cell infiltrate [16]. Diagnostic separation of these two lymphoid neoplasias has clinical significance due to their well-documented differences in clinical course and in optimal therapeutic approach [1]. Because a significant fraction of cHL is associated with EBV infection in elderly patients, the diagnostic distinction between EBV+ DLBCL of the elderly and EBV+ cHL relies essentially on immunophenotyping. A typical immunophenotypic profile of RS cells, or their variants, in cHL is characterized by the expression of CD30 and CD15 and the down-regulation of B-cell antigens and leukocyte common antigen CD45 [17]. Therefore, its distinction from EBV+ DLBCL of the elderly is not problematic in the majority of the cases because of the expression of B-cell antigens and absence of CD15 in the latter [1,10–12,16]. To the best of our knowledge, a true gray zone lymphoma with hybrid features of EBV+ cHL and EBV+ DLBCL of the elderly in both morphology and immunophenotypic profile has not been reported in the English

* Corresponding author at: Department of Pathology, DUMC Box 3712, M-345 Davison Bldg (Green Zone), Duke Hospital South, Durham, NC 27710, United States. Tel.: +1 919 681 8426; fax: +1 919 684 1856.
E-mail address: endi.wang@duke.edu (E. Wang).

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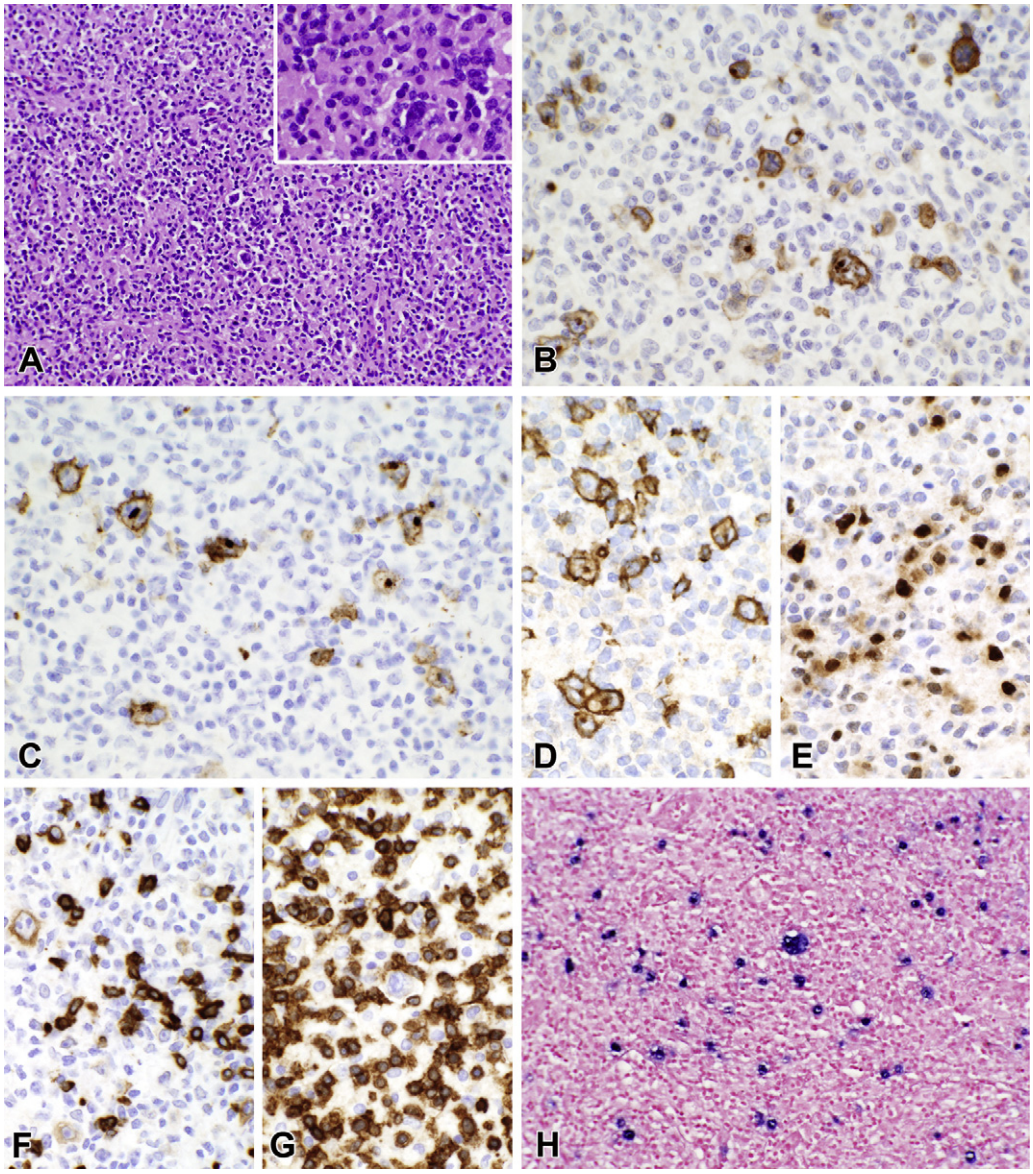

Fig. 1. (A) The left inguinal lymph node biopsy showing nodal architecture effaced by proliferation of heterogeneous cells, including scattered large pleomorphic cells, H&E stain, 200×. Inset indicates three pleomorphic large cells with Reed–Sternberg cell-like morphology, H&E stain, 400×; (B) Immunohistochemical stain with antibody against CD30 showing strong positivity in pleomorphic large cells with membrane/Golgi zone staining pattern, 400×; (C) CD15 positivity in the pleomorphic large cells with membrane/Golgi zone staining pattern, 400×; (D) The pleomorphic large cells are positive for CD19, 400×; (E) OCT2 stain, 400×. Note a positive nuclear staining in pleomorphic large cells and a few smaller cells; (F) CD79a stain, 400×. Note weaker staining in pleomorphic large cells and strong staining in more small to medium-sized lymphoid cells; (G) CD3 stain, 400×. Note many positive small to medium-sized cells and distinctive negativity in pleomorphic large cells; (H) EBER ISH showing positive nuclear staining in a heterogeneous population of cells, including a few pleomorphic large cells and many smaller bystander cells, 200×.

literature. Here, we describe a case of EBV+ malignant lymphoma of B-cell origin in a 67-year-old female with morphologic features and immunophenotypic profile overlapping between EBV+ DLBCL of the elderly and EBV+ cHL.

Case report

The patient, a 67-year-old female with an unremarkable past medical history, presented to her physician with progressive fatigue, malaise, low-grade fever and weight loss (22 pounds over 2 months). A physical examination revealed left supraclavicular, right axillary and bilateral inguinal lymphadenopathy. In addition to the lymphadenopathy identified by physical exam, computed tomography (CT) scan demonstrated multiple internal lymphadenopathies, including enlarged mediastinal, mesenteric, retroperitoneal and pelvic lymph nodes. CT/Positron emission tomography (PET) scan showed multiple diffuse foci of fluorine-18 2-fluoro-2-deoxyglucose (FDG) uptake with standard uptake value (SUV) up to 30. These include involvement of multiple bony lesions, spleen, bilateral kidneys, as well as the aforementioned lymph nodes. Laboratory tests revealed elevated serum lactate dehydrogenase (LDH) to 453 U/L (reference range, 100–200), mild to moderate anemia (hemoglobin 10.9 g/dl, hematocrit 34%) and slightly decreased blood leukocyte count (2300 μl^{-1}) with 59% neutrophils and 25% lymphocytes. Biopsy of the left inguinal lymph node demonstrated findings consistent with EBV-positive malignant lymphoma of B-cell origin. The staging bone marrow examination showed findings consistent with lymphomatous involvement. The patient was thus considered to be stage IV. She underwent 5 courses of BEACOPP (Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone) chemotherapy. Approximately one year after the