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Case study

Rare variants in the spectrum of human herpesvirus 8/Epstein-Barr virus–copositive lymphoproliferations

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Summary We report 2 rare variants in the spectrum of human herpesvirus 8 (HHV8)/Epstein-Barr virus (EBV)–copositive lymphoproliferations arising in HIV-seronegative patients, including a large B-cell lymphoma arising in the setting of multicentric Castleman disease and a germinotropic lymphoproliferative disorder. In the first case, histology revealed features of multicentric Castleman disease and a proliferation of large lymphoid cells forming clusters or arcs or rings replacing the periphery of follicles or sheets of frank lymphoma outside the follicles. In the second case, a proliferation of large lymphoid cells totally or partially invaded follicle germinal centers. In both cases, the large cells were positive for EBV-encoded small RNA, HHV8 (LANA-1), MUM1/IRF4, and CD38 and negative for CD45, CD79a, CD10, BCL6, and CD138. In the large B-cell lymphoma, the large cells did not express detectable cytoplasmic immunoglobulin light- and heavy-chains, whereas in the germinotropic lymphoproliferative disorder, the large cells expressed μ heavy chain. The present cases broaden the spectrum of HHV-EBV–copositive lymphoproliferations.

1. Introduction

Human herpesvirus 8 (HHV8) is associated with several lymphoproliferative disorders such as primary effusion lymphoma (PEL), extracavitary solid PEL, germinotropic lymphoproliferative disorder (GLPD), multicentric Castleman's disease (MCD), and MCD-associated plasmablastic lymphoma or large B-cell lymphoma (LBL) arising in HHV8-associated MCD [1–14]. These disorders, with the exception of GLPD, arise more frequently in immunodeficient patients [1–14]. LBL arising in HHV8-associated MCD is usually associated with human immunodeficiency virus (HIV) but not with Epstein-Barr virus (EBV) infection [1–5,10,11,14]. We report an unusual case of an EBV-positive LBL arising in HHV8-associated MCD, which occurred in an HIV-negative patient. We also report a case of GLPD, which is a very rare HHV8-EBV–copositive entity because, to the best of our knowledge, only 7 cases have been reported so far in the English-language literature (reviewed by Courville et al [14]).

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2. Report of 2 cases

2.1. Case 1

A 79-year-old man was referred to the Hematology Department, University Hospital of Ioannina, due to fatigue, anemia, and splenomegaly. He had a medical history of diabetes mellitus over the last 15 years and coronary artery disease (coronary artery bypass grafting 3 years ago). On physical examination, he was pale and had cervical, axillary, and inguinal lymphadenopathy bilaterally, splenomegaly and lower limb edema. Laboratory tests were as follows: hemoglobin, 9.7 g/dl; hematocrit, 30%; white blood cell count, 9.78×10^9/L (differential count: neutrophils 6.1×10^9/L, lymphocytes 2.77×10^9/L, monocytes 0.9×10^9/L); platelet count, 116×10^9/L; erythrocyte sedimentation rate, 74; creatinine, 1.6 mg/dL; urea, 103 mg/dL; albumin, 2.8 mg/dL; β_2-microglobulin, 6104 μg/L; and diffuse hypergammaglobulinemia. Computed tomographic scans revealed generalized lymphadenopathy (cervical, axillary, mediastinal, retroperitoneal, and inguinal) and splenomegaly. Extensive workup for infectious or autoimmune diseases was negative, so an axillary lymph node biopsy was performed.

2.2. Case 2

A 53-year-old man was referred to the Hematology Department, University Hospital of Ioannina, complaining of swelling of cervical nodes on both sides of the neck. He had no constitutional symptoms. Physical examination revealed supraclavicular lymphadenopathy on the right side of the neck. Ultrasound of the heart was normal. Laboratory tests were within normal limits, and only the hepatic enzymes serum glutamic oxaloacetic transaminase of 43 IU/L and serum glutamic pyruvic transaminase of 39 IU/L were elevated. Computed tomographic scans revealed a block of supraclavicular lymph nodes on the right side of the neck, smaller lymph nodes on the left side of the neck, and fatty infiltration of the liver. A cervical lymph node biopsy was performed.

3. Materials and methods

The tissue was fixed in 10% buffered formalin and processed as usual for paraffin embedding. Immunostainings were performed on the Ventana Benchmark autostainer (Ventana Medical Systems, Tucson, AZ) on paraffin-embedded sections using the Ventana diaminobenzidine tetrahydrochloride kit according to the manufacturer's instructions. The following antibodies were used: HHV8, CD79a, CD45, CD5, and BCL2 (Cell Marque, USA); CD30, MUM1/IRF4, BCL6, and P53 (Dako); CD38 (Neomarkers, USA); CD138, CD20, PAX5, CD8, CD23, and CD21 (Biogenex, USA); CD10 (Leica, Novocastra, USA); Ki-67 (Biocare, USA); and CD3 and CD4 (Spring, USA). EBV-encoded small RNAs (EBERs) in situ hybridization was performed with the kit Bond Ready-to-Use ISH EBER Probe Catalog No. PB0589 (Leica Biosystems, USA).

4. Results

4.1. Case 1

4.1.1. Lymph node biopsy findings

The excised axillary lymph node measured $3 \times 2.3 \times 1.6$ cm. Histologic examination of hematoxylin-eosin (HE)–stained sections showed classical features of MCD including follicles with variable degrees of regression, hyalinization, and mantle zone expansion. The interfollicular area had a dense infiltrate of plasma cells and increased numbers of blood vessels. The sinuses were patent. In addition, the lymph node was partially infiltrated by a proliferation of large lymphoid cells including some with round or oval nuclei with the appearance of plasmablasts or immunoblasts and some with irregular nuclear contours. In some regions, the large lymphoid cells formed clusters adjacent to follicles or in the mantle zones of follicles. In other regions, the large lymphoid cells formed arcs or rings replacing the periphery of follicles or nodules possibly resulting from total replacement of follicles or frank lymphoma composed of diffuse sheets of large cells outside the follicles (Fig. 1). Immunohistochemical studies showed that the large lymphoid cells were positive for HHV8 (LANA-1), MUM1/IRF4, CD38, and CD30 and negative for CD138, CD45, CD20, CD79a, PAX5, CD5, CD3, CD4, CD8, CD10, CD15, BCL6, BCL2, and EBV-encoded LMP-1 (Fig. 1). Ki-67 stained 90% of large lymphoid cells. LANA-1, MUM1, and CD38 immunostainings highlight the arc-like distribution of the large lymphoid cells around the follicle and an area of frank lymphoma (Fig. 1). The large lymphoid cells did not express immunoglobulin heavy or light chains, whereas intrerfollicular plasma cells were MUM1+ and CD138+, and expressed γ, α and μ heavy chains and polytypic light chains (κ+ and λ+). The large lymphoid cells were positive for EBER by situ hybridization (Fig. 1).

4.1.2. Bone marrow biopsy findings

Histologic examination revealed hypercellular marrow with trilineage hematopoiesis and without infiltration by large lymphoid cells. Immunohistochemical examination revealed numerous CD138-positive small aggregates of plasma cells with polytypic light-chain expression and scattered or small aggregates of small B cells with CD20 and PAX5 positivity.