A Rare Case of Metachronous Peripheral T-Cell Non-Hodgkin Lymphoma Following Epstein Barr Virus-Positive Diffuse Large B-Cell Lymphoma, Not Otherwise Specified

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Received: 1 August 2021
Accepted: 14 October 2021

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DOI 10.5001/omj.2023.13

Abstract

Epstein Barr virus - positive (EBV+) diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS), is a newly recognized rare aggressive B- cell neoplasm with a wide morphologic spectrum. Metachronously developed B- cell and T- cell composite lymphoma (CL) is quite rare. We report a case of an elderly male who presented with enlarged abdominal lymph nodes and diagnosed as EBV+ DLBCL, NOS. He was started on chemotherapy which had to be discontinued after three cycles due to life threatening Pneumocystis carinii pneumonia and poor performance status. While on follow up, within two years, the patient presented with features of relapse. A repeat histopathological examination of the lymph node showed features of Peripheral T cell lymphoma, not otherwise specified (PTCL, NOS) and the clonality was confirmed by T- cell receptor gamma chain rearrangement assay. More studies are needed to understand the association of EBV+ DLBCL, NOS with other lymphomas.

Keywords: Epstein Barr virus - positive diffuse large B-cell lymphoma, not otherwise specified; composite lymphoma; metachronous

Introduction

Epstein Barr virus - positive (EBV+) diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS), is a newly recognized aggressive B-cell lymphoma associated with chronic EBV infection.[1] The World Health Organisation (WHO) recognizes a pathologic spectrum ranging from a monomorphic pattern with a predominance of large cells to a more common polymorphous subtype characterised by scattered large cells amidst a reactive background.[2,3] The large cells may appear as centroblasts, immunoblasts or as Hodgkin and Reed-Sternberg (HRS) like cells. Montes-Moreno et al. described three morphologic subgroups: one called large cell type composed of numerous large cells, another showing HRS-like large cells resembling classic Hodgkin Lymphoma (cHL), and a third subtype resembling T- cell/histiocyte-rich large B-cell lymphoma showing only few or no HRS-like cells.[4]

Composite lymphoma (CL) is defined as two or more distinct lymphoid neoplasms that occur in the same site.[5,6] CL is very rare, with a reported frequency ranging from 1 to 4.7 % of all lymphoma cases.[7] It can occur in various combinations, including composite B-cell lymphoma, composite B- and T-cell lymphoma, and composite Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).[6] It can develop synchronously or metachronously.[8-10] A diffuse large B-cell lymphoma developing metachronously in nodular lymphocyte predominant HL is the commonest type of CL.[10] In some cases of composite lymphomas, polymerase chain reaction (PCR) amplification and sequence analysis of the immunoglobulin heavy chain gene (IGH) demonstrated common clonal origins.[11,12] It is thought to be of common precursor cell origin which are genetically identical but morphologically different due to different transformation events.[8] Metachronously developed cases may be due to complications of previous chemotherapy associated with immune dysregulation.

We report an unusual case of Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) that seemed to develop metachronously in the patient with EBV+ DLBCL, NOS with HRS like cells.

Case Report

A 70 year old hypertensive male presented with fatigue and cough with minimal expectoration for 3 months, not associated with fever or night sweats. He also reported history of undocumented weight loss. On physical examination, he was found to have enlarged axillary lymph nodes and mild splenomegaly. Hemogram and peripheral blood smear examination showed normochromic anemia with leucopenia and mild thrombocytopenia. His serum LDH and uric acid levels were mildly elevated. Radiological imaging studies confirmed splenomegaly and additionally revealed the presence of enlarged paraaortic and peripancreatic nodes. Bone marrow examination was done in view of pancytopenia and was found to be normal. Histopathological examination of the left axillary lymph node showed features of reactive hyperplasia and was followed by laparoscopic para-aortic lymph node biopsy. The lymph node was 3x2 cm in size with a homogenous, grey white cut surface. Microscopic sections showed small lymphocytes arranged in a nodular pattern with many scattered large mononuclear, multilobed and multinucleated cells having abundant cytoplasm and vesicular nuclei with prominent eosinophilic nucleoli. A few lacunar cells, mummified cells and clusters of histiocytes were also seen (figure 1). The large cells were CD30, CD20 and PAX5 positive, and LCA, CD3 and CD15 negative. A mixture of CD20 & CD3 positive lymphocytes formed the background population. A second panel of immunostains performed showed diffuse strong positivity for EBV-LMP1 , MUM1 and BOB1, weak positivity for OCT2 and fascin negativity in the large cells. MIB-1 proliferation index was 80% (figure 2). Epstein-Barr encoding region (EBER) in situ hybridization was not done due to logistic reasons. A final impression of EBV+DLBCL, NOS was rendered.

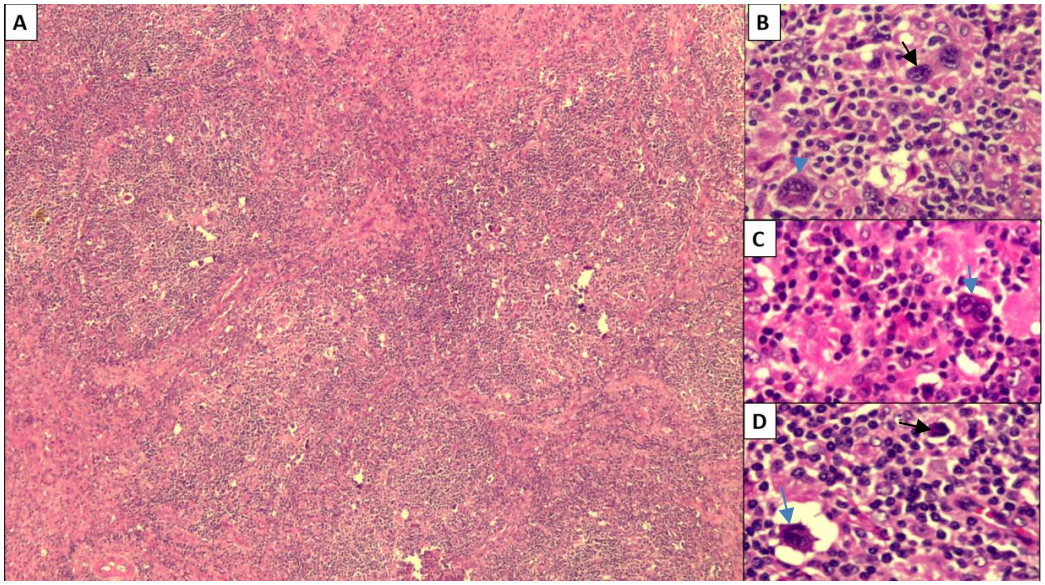

Figure 1 : A. Para-aortic lymph node biopsy showing small lymphocytes arranged in nodular pattern with many scattered large cells (H&E, x100) ; B. Large mononuclear cells (black arrow) and multinucleated giant cells (blue arrow) (H&E, x400) ; C. Classic Reed Sternberg (RS) like cells (blue arrow) (H&E, x400) ; D. A few lacunar cells (blue arrow) and mummified cells (black arrow). Background showed small lymphocytes (H&E, x400)

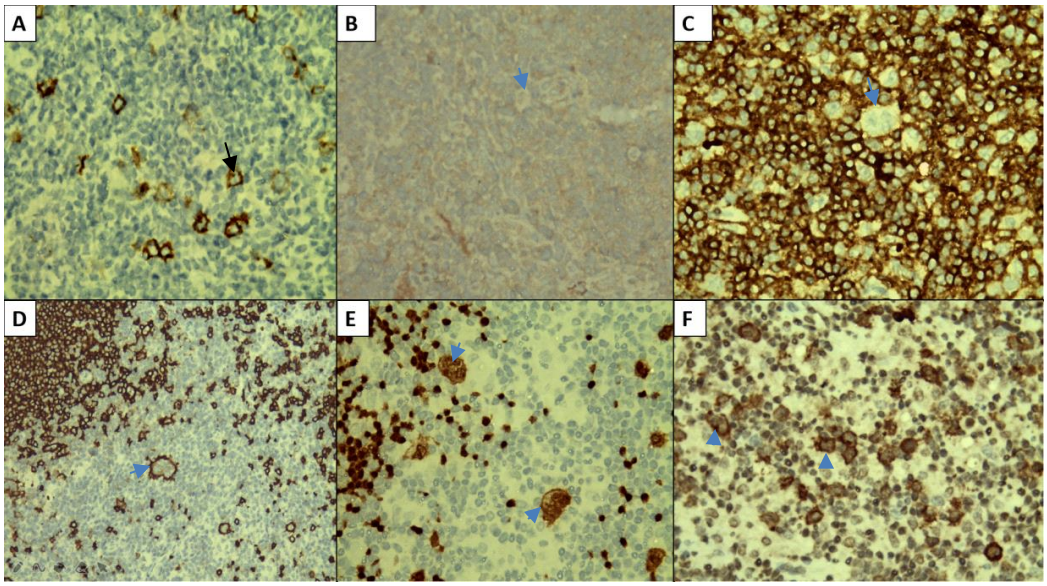

Figure 2 : A. The large cells were positive for CD30 (CD30, x400); B. The large cells were negative for CD15 (CD15, x400); C. The large cells were negative for LCA (LCA, x400); D. The large cells were positive for CD20 (CD20, x400); E. The large cells were positive for PAX5 (PAX5, x400); F. The large cells were positive for EBV-LMP1 (EBV-LMP1, x400)

PET CT showed FDG avid multiple supra and infradiaphragmmatic lymph nodes, spleen and marrow spaces of axial skeleton (Ann Arbor Stage IV). Quantitative polymerase chain reaction for EBV done on blood detected 19,959 copies/ml. He was worked up to rule out immunodeficiency and autoimmune diseases. Patient was planned for R mini CHOP 21 x 6 cycles. After 3 cycles, patient attained complete FDG PET metabolic response and molecular complete remission. As the patient developed severe Pneumocystis carinii pneumonia and severe renal failure, chemotherapy was discontinued and he was started on Rituximab maintenance.

A year and a half later, the patient presented with a three days history of low backache and abdominal pain. Ultrasonogram revealed borderline splenomegaly and multiple intra-abdominal enlarged lymph nodes with perinodal fat stranding. Whole body PET CT imaging revealed FDG avid right axillary & deep pectoral, para-aortic, aortocaval, retrocaval, mesenteric and iliac nodes. Trucut biopsy of the axillary and para aortic lymph nodes showed a dense infiltrate composed of lymphoid cells, histiocytes, plasma cells and neutrophils. The lymphoid cells were intermediate sized with scant to moderate cytoplasm, clumped to vesicular nuclei with irregular to clefted nuclear contours and inconspicuous nucleoli. A few ill formed histiocytic collections were also seen (figure 3). Special stains for acid fast bacilli and fungal organisms were non-contributory. Immunohistochemical stains showed that the intermediate sized lymphoid cells were positive for CD3, CD5 and CD4, and were negative for CD7, CD8, CD10, CD20, CD56, CD30, PAX5, MUM1, BCL6 and EBV LMP1. Ki 67 proliferation index was about 50%.

The histomorphological and immunohistochemical findings were suggestive of PTCL, NOS. T- cell receptor gamma chain gene rearrangement assay confirmed the clonal nature of the T cell population. The patient was started on chemotherapy with CVP (Cyclophosphamide, Vincristine, Prednisolone) protocol, however he succumbed to his illness.

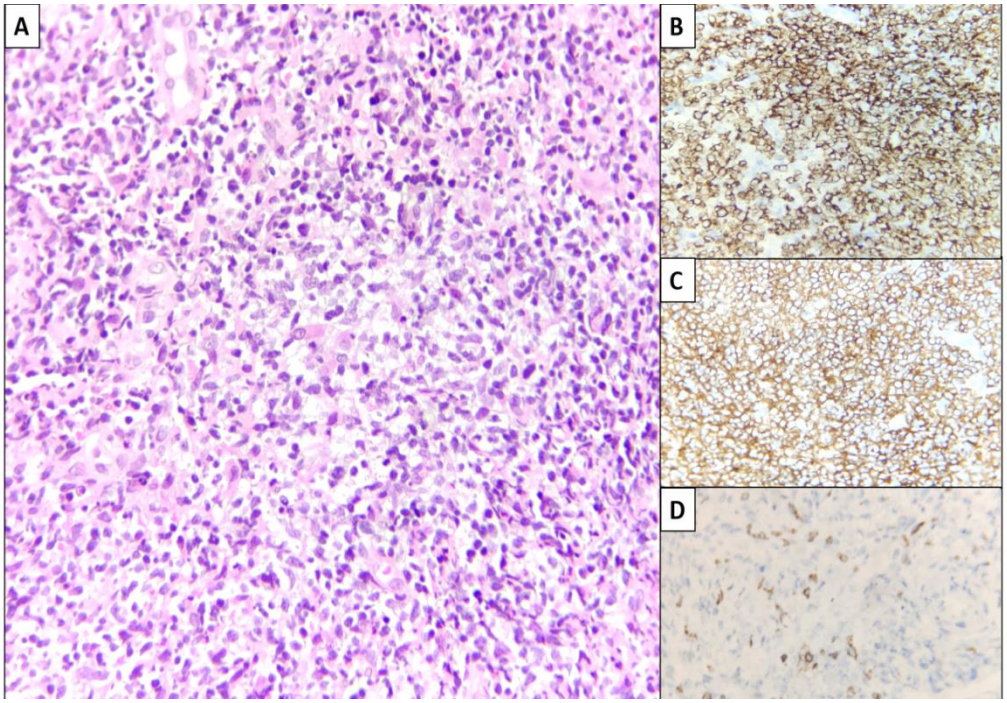

Figure 3: A. Right axillary lymph node biopsy showing dense infiltrate composed of lymphoid cells, histiocytes, plasma cells and neutrophils. The lymphoid cells were intermediate sized with scant to moderate cytoplasm, irregular to clefted nuclear contours and inconspicuous nucleoli.(H&E, x400) ; B. The atypical cells were positive for CD3 (CD3, x400), C. Positive for CD4 (CD4, x400), and D. Negative for CD8. (CD8, x400)

Discussion

EBV+ DLBCL, NOS is a distinct lymphoid neoplasm recognized in the revised 4th edition of the 2016 classification of the World Health Organization (WHO) which is associated with a poor response to chemotherapy and short survival.[1] It was previously designated as EBV-positive DLBCL of the elderly as most patients tended to be elderly. Of late, it has been reported over a wide age range, and is more common among Asian and Latin American patients compared to western patients.[13, 14] Involvement can be nodal or extranodal , the most common extranodal sites being lungs and gastrointestinal tract.[14] The neoplastic component in some cases consists of a variable number of large transformed cells on a background of mixed population of small lymphocytes, plasma cells, histiocytes, and eosinophils imparting a morphologic overlap with classic Hodgkin lymphoma. When the background reactive component is rich in small lymphocytes and histiocytes, the so called polymorphic pattern, resembling T-cell/histiocyte-rich large B-cell lymphoma, is the most common pattern in young patients.[15] The monomorphic pattern can be distinguished from EBV-negative DLBCL with ancillary studies only. The neoplastic cells are typically positive for the pan-B-cell antigens with an activated-B-cell immunophenotype.[14] CD30 is usually positive with occasional CD15 co expression, but lack other phenotypic features typical of classic Hodgkin lymphoma. The disease has an aggressive course, even when treated with combination chemotherapy. [16]

CL is an uncommon lymphoid malignancy with a variety of patterns. The most common types are B-cell non Hodgkin lymphoma composite with a Hodgkin lymphoma or two composite B-cell non Hodgkin lymphomas of different types.[6] CL consisting of B-cell and T-cell neoplasms are extremely rare constituting less than 1% of all lymphoid malignancies and the pathologic features of this type have not been well characterized.[17] Among the reported cases of this subtype, the T-cell neoplasms were most often PTCL, NOS whereas the B-cell components were diverse with DLBCL being most frequent followed by marginal zone lymphoma and other low grade B- cell lymphomas, Hodgkin lymphoma and plasmacytoma. Most of these cases were of nodal origin, whereas in a minority of cases, they arose in extranodal tissues.

Though the exact pathogenesis of CL remains unclear, a few hypothetical mechanisms have been proposed.[18] One possible etiology of CL is viral induced transformation of two or more separate neoplastic clones. This oncogenic activity has been observed most frequently in EBV in immunocompromised patients. EBV-related large B-cell lymphoma has been described in association with PTCL and angioimmunoblastic T cell lymphoma (AITL) in a simultaneous or sequential occurrence.[19] It has been thought that EBV antigens expressed in host B cells may stimulate T-cell proliferation and eventually induce neoplastic transformation of T cells, via a process of clonal selection.

Another hypothesis is, immunodeficiency associated with T-cell malignancy predisposing to EBV infection which in turn causes clonal transformation of B cells in the host.[20]

This case report adds to our knowledge of the natural history of EBV+ DLBCL, NOS which is a newly described entity. Further studies are required to understand the pathogenesis of metachronous EBV+ DLBCL, NOS and PTCL.

Conclusion

We report a noteworthy case of EBV+ DLBCL, NOS, which initially presented as intra-abdominal lymphadenopathy with metachronous development of PTCL, NOS. Being a newly recognised entity, more data about the course of the disease is required.

Consent statement

Institutional ethics committee waived the consent [RAJH/A/2021/004].

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