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Hepatic Localization of Diffuse B-Cell Lymphoma with Large EBV-Positive Cells on Hodgkin's disease History: A Case Report

M. R. EL Ochi[1,3*], E. M. Mahtat[2, 3], A. Kessab[1, 3], M. Azakhmam[1,3], M. A. Essaoudi[1,3], A. El Ktaibi[1,3], K. Doghmi[2,3], M Oukabli[1,3], A Albouzidi[1,3]

[1]Department of Anatomy and Pathological Cytology of Mohammed V Military Hospital, Rabat Rabat, Morocco
[2]Hematology Department of Mohammed V Military Hospital, Rabat Rabat, Morocco
[3]Faculty of Medicine and Pharmacy, Mohammed V University, Rabat Rabat, Morocco

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***Corresponding author:** Mohammed Reda EL OCHI

Abstract **Case Report**

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 63-year-old patient followed since 2015 for mixed Stage IIIB, IPS-3 Hodgkin lymphoma. Initially treated with 6 BEACOPPe procedures, with partial remission at the end**.** The disease remained in control until July 2019, when the patient presents with general signs (night sweats and slimming). The clinical examination finds isolated hepatomegaly. Following hepatic biopsy, analysis of morphological data and immunohistochemical study results, especially the intense and diffuse CD20 positivity and the negativity of CD15, led to the diagnosis of EBV-positive EBV positive EBV-positive large B-cell lymphoma. It has been documented that EBV plays a crucial role in the pathogenesis of both cHL and some cases of DLBCL, particularly in immune compromised patients [14, 17, 18]. However, the detailed mechanisms by which the virus transforms the B-cells into two distinctive lymphoid neoplasms remain to be elucidated.

Keywords: EBV, Lymphoma, DLBCL, Hepatic.

INTRODUCTION

Diffuse large-cell Epstein-Barr virus-positive B lymphoma is defined as an EBV-positive monocellular B cells lymphoid proliferation according to the revised classification of hematopoietic and lymphoid tissue tumors of the World Health Organization as revised 2017.

This lymphoma generally affects individuals over 50 years old, especially in an immunosuppression field; however, a few cases have been described in young patients with no concept of immunodeficiency.

Treatment remains that of NOS large-cell diffuse B-cell lymphoma due to a lack of standardized therapy for this entity. Therefore, trials with new therapies need to be put on the agenda to improve the prognosis, such as antiviral treatments, specific inhibitors of the transmission pathways (NF-kB pathway eg) and the adoptive immunotherapy.

PRESENTATION CASE

A 63-year-old patient followed since 2015 for mixed cellularity stage IIIB, IPS 3 Hodgkin lymphoma. Initially treated with 6 BEACOPPe procedures, with partial remission at the end. Catch-up with 4 DHAOX cures with a complete remission at the end (04/11/2015). The patient did not get an intensification for lack of care. The disease remained in control until July 2019, when the patient presents with general signs (night sweats and slimming). The clinical examination finds isolated hepatomegaly. The PET scanner shows disseminated pathologic and hyper-metabolic hepatic foci with a max SUV of 29.4, splenic foci (SUV max 18.2), bony in the costal grill (max SUV 8.3).

Hepatic biopsy was performed and showed hepatic parenchyma with lymphomatous proliferation of large cells, mixed with sterbergoids and giant cells (Figure 1). The background is granulomatous epithelioid cells rich in lymphocytes and plasma cells (Figure 2).

An immunohistochemical study was done to characterize the nature of lymphoid cells and showed the following results (Figures 3,4 and 5):

- Diffuse staining of the tumor cells for the anti-CD20 antibody;
- Positive staining of large tumor cells for anti-CD30, anti-EBV, and anti-MUM1 antibodies;
- No labeling of tumor cells for anti-CD15, anti-CD5 and anti-EMA antibodies.

The morphological data and immunohistochemical study results, especially the intense and diffuse CD20 positivity and the CD15 negativity, have been directed towards the diagnosis of EBV positive DLBCL positive large B-cell lymphoma.

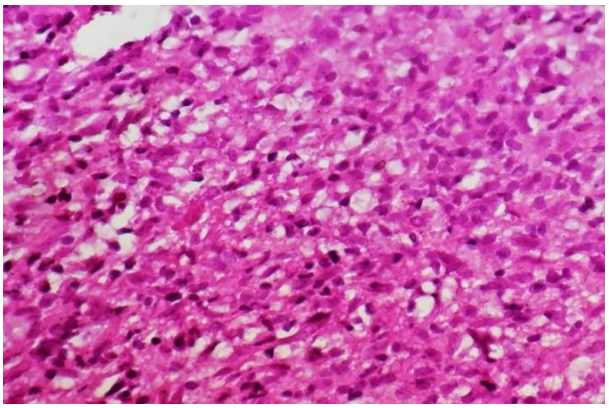

Fig-1: Histological image showing the hepatic parenchyma with lymphomatous proliferation of large cells, mixed with sterbergoids and giant cells Gx400

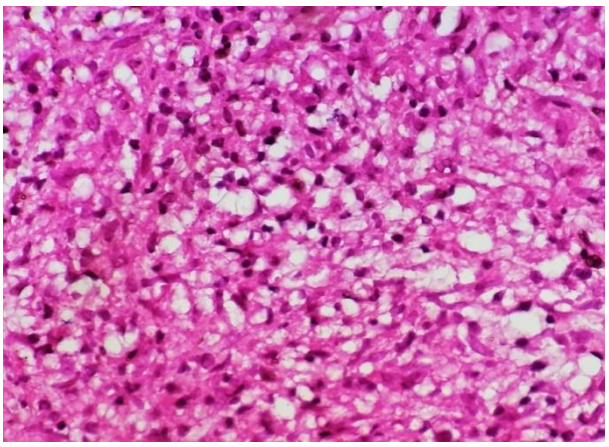

Fig-2: Histological image showing the background is granulomatous epithelioid cells rich in lymphocytes and plasma cells Gx400

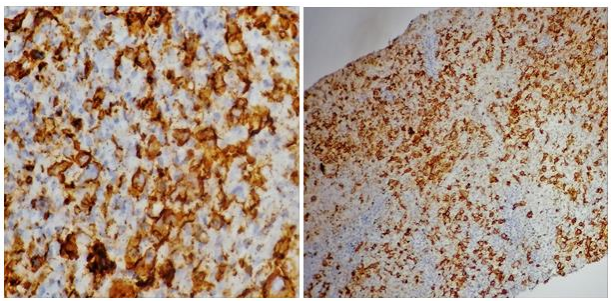

Fig-3: Diffuse staining of the tumor cells for the anti-CD20 antibody

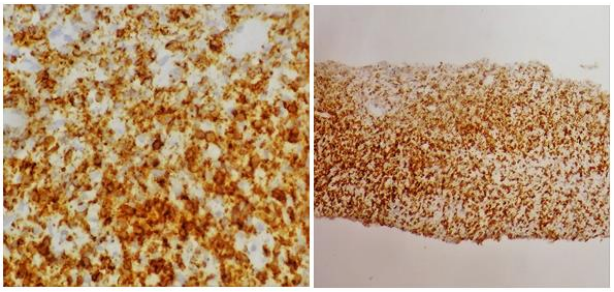

Fig-4: Positive staining of large tumor cells for anti-CD30 antibodies

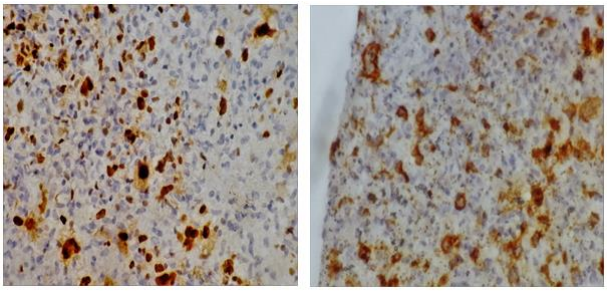

Fig-5: Positive staining of large tumor cells for anti-EBV, and anti-MUM1 antibodies

DISCUSSION

Epstein Barr (EBV1) non-specific (NOS) diffuse large cell lymphoma B is a clinical-pathological entity recognized in the revised 4th edition of the 2016 World Health Organization (WHO) classification [1]. Oyama and AL reported in 2003 on 22 patients with large cell lymphoma an expression of RNA encoding EBV (EBER) in malignant cells nuclei [2,3].

These patients are all elderly and have low response to standard chemotherapy with short survival. In recent years, this type of lymphoma has been observed in younger patients. EBV infection is common worldwide with prevalence ranging from 80 to 95%, depending on the geographical area. In the case of patients with DLBCL, the prevalence of EBV infection is unknown.

However, small studies and case series gave different results with prevalence rates of 5% in Western countries and 10% to 15% in Asia and South America [4, 5]. The reasons for this difference are not clear, but it is probably because of the role of virologic (for

example, the EBV strain) and genetic factors (eg, HLA types).

EBV is a double-stranded, enveloped virus that belongs to the family Herpesviridae. It shows a tropism for epithelial cells as well as B cells [6, 7]. Almost all humans are exposed to EBV at some point in their lives with latency after exposure. This can cause problems in the aging population. With age, the immune system goes into a state of immunosenescence characterized by a decrease in B cell diversity, causing clonal expansion in vivo.

Clinically, patients tend to be diagnosed at a later age; hence the old name for the term "elderly subjects". In addition to ganglionic damage demonstrated by high score of International Prognostic Index (IPI), patients tend to have extra-ganglionic manifestations especially in the gastrointestinal tract, skin, and bone marrow. In addition, high LDH and late-stage clinical discovery are more common in EBV-positive patients than in other large B-cell lymphomas.

Expectedly, the definition of EBV1 DLBCL, NOS, continues to evolve. Recent evidence shows that EBV1 DLBCL, NOS, can be seen in young, and immunocompetent [9-10]. These studies have shown that the virological and pathological results are similar in young and old, which explains the change of the name in the new WHO classification. It is important to note that there is no clear limit for a positive expression of EBER proven by recent studies [11].

The immunohistochemical profile of this type of lymphoma is important for diagnosis and is generally positive for B cell markers: CD20, CD19, CD79a and PAX-5. CD10 and BCL6 antibodies are generally negative, whereas MUM1 is commonly positive. Cases with immunoblastic or plasmablastic differentiation may be negative for CD20 [12]. In situ hybridization for EBER is positive and is considered the most important diagnostic confirmation test, with high sensitivity [7].

DLBCL EBV + is characterized by a poor response to treatment, hence the need for rapid detection. Detection is based on clinical suspicion and looking for EBV in all cases of DLBCL.

The prognosis of DLBCL EBV + is worse than that of EBV-negative tumors, with a median survival of 2 years [12, 13]. Age plays an important role with decreased survival in patients over 70 years old. Currently, there is no uniformly accepted treatment except the standard chemotherapy proposed for DLBCL NOS [7, 13].

The group of B-cell neoplasms associated with EBV infection has increased exponentially, and before a diagnosis of EBV1 DLBCL, NOS, is made, there are several diseases that need to be eliminated, so in many cases, EBV1 DLBCL, NOS, is an exclusion diagnosis. The entities to exclude are those with apparent immunosuppression, such as patients with post-transplantation lymphoproliferation (PTLD) [14], patients with induced iatrogenic immunosuppression such as those receiving methotrexate or tumor necrosis inhibitory factors [15], and patients infected with HIV. In addition, there are entities associated with EBV infection, such as lymphomatoid granulomatosis characterized by angiocentric lesions involving the skin, lungs or central nervous system [16,17]; DLBCL in patients with chronic inflammation [18]. Classic Hodgkin's Lymphoma should also be taken into account because of its variable association with EBV infection.

EBV has been shown to play a crucial role in the pathogenesis of Hodgkin's lymphomas and in a few cases of DLBCL, particularly in immunocompromised patients [19-21]. However, the mechanisms by which the virus transforms B cells into two distinctive lymphoid neoplasms remain to be elucidated.

Future studies of the stage of EBV B cell infection and associated changes in gene expression, immunophenotyping, and morphology may explain the pathogenesis leading to these two phenotypically and morphologically distinct lymphomas.

CONCLUSION

Very numerous associations between EBV and lymphoid proliferations have recently been reported, with the detection of the viral genome within the tumor population. The infected cells are of different nature, stage of differentiation and functional states. EBV can thus infect B cells before the immunoglobulin gene rearrangement stage [22], disrupting their maturation and rendering them incapable of expressing the immunoglobulin heavy chains [23].

Immature cells can acquire, after infection, an activated cell phenotype, EBV likely playing a role in these pathological changes. In addition, under certain conditions, many inflammatory cells identical to those of Hodgkin's disease may be associated with lymphomatous proliferation. These phenomena may explain the appearance of composite lymphoma associating NHL and Hodgkin's disease where EBV is involved. Thus, the morphological, immunophenotypic and anatomo-clinical aspects of lymphoid proliferations may result not only from the nature of the target cell, but also from interactions with viral factors, such as EBV, and the immune status of the host.

ABREVIATIONS

EBV1 DLBCL: Diffuse large-cell Epstein-Barr virus-positive B lymphoma
cHL: classical Hodgkin lymphoma
NOS: non-specific
IPI: International Prognostic Index

WHO: World Health Organization

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work has respected all the rools of medical ethics and has been elaborated by all the authors.

AVAILABILITY OF MATERIAL AND DATA

All data is available in the military hospital Mohammed V, Rabat, Morocco.

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CONSENT TO PUBLISH

As the main author and the names of all authors I allow you to publish this article in your review

COMPETING INTERESTS

The authors do not declare any conflict of interest.

AUTHOR'S CONTRIBUTIONS

All the authors contributed to the writing of this work.

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