



EBV-positive follicular lymphoma and concurrent EBV-negative diffuse large B-cell lymphoma illustrating branched evolution model and “Hit and Run” hypothesis

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Abstract

Epstein-Barr virus (EBV) is one of the most common viruses associated with multiple malignancies including hematopoietic, epithelial, and mesenchymal neoplasms. EBV is linked to B- and T-cell lymphomas, ranging from indolent to highly aggressive neoplasms. EBV-positive follicular lymphoma (FL) is not well characterized due to its low prevalence. In this report, we describe a case of EBV-positive FL and concurrent EBV-negative diffuse large B-cell lymphoma (DLBCL), and discuss their clonal relationship, and EBV status in the process of disease progression. Histology, immunohistochemistry, in situ hybridization, and next-generation sequencing studies were performed as previously described. The 58-year-old male presented with extensive axillary and subpectoral lymphadenopathy. The patient had a history of mixed connective tissue disease treated in the past with steroids and methotrexate, and at the time of current presentation with hydroxychloroquine. The excision of axillary lymph node showed coexistent EBV-positive FL (grade 3B) and EBV-negative DLBCL. There was no evidence of *BCL2* gene rearrangement; however, both EBV-positive neoplastic follicles and diffuse component harbored *MYC/IGH* rearrangement. Next-generation sequencing suggested branching evolution with shared *DDX3X* mutation, a number of private mutations, and unique *IGH* usage in FL and DLBCL. The patient was treated with six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) with involved-field radiotherapy and remains in complete remission. To the best of our knowledge, this is the first report of *BCL2* rearrangement negative, *MYC/IGH*-positive and EBV-positive FL, and concurrent EBV-negative DLBCL, which supports branched evolution model.

Keywords Follicular lymphoma · Diffuse large B-cell lymphoma · Epstein-Barr virus · MYC · Branched evolution · Hit-and-run hypothesis

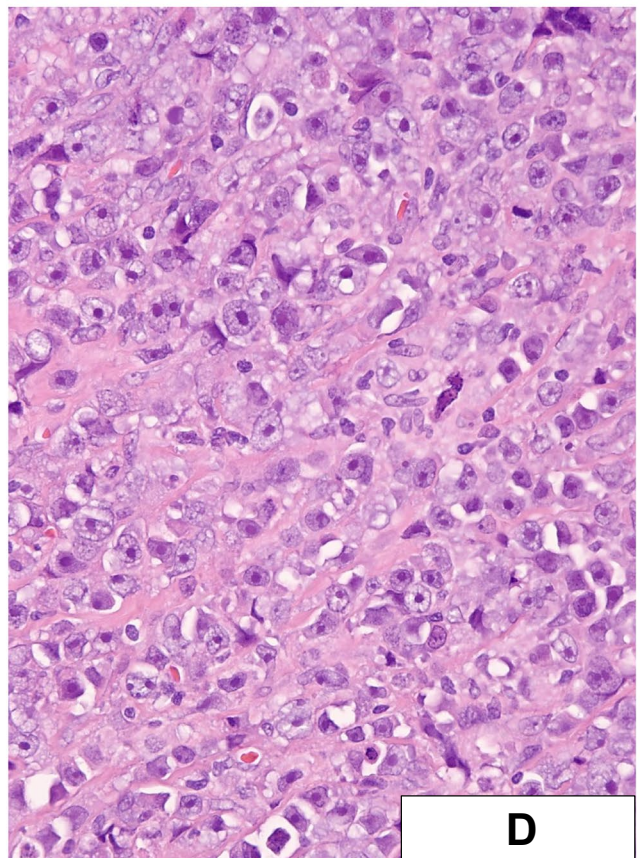
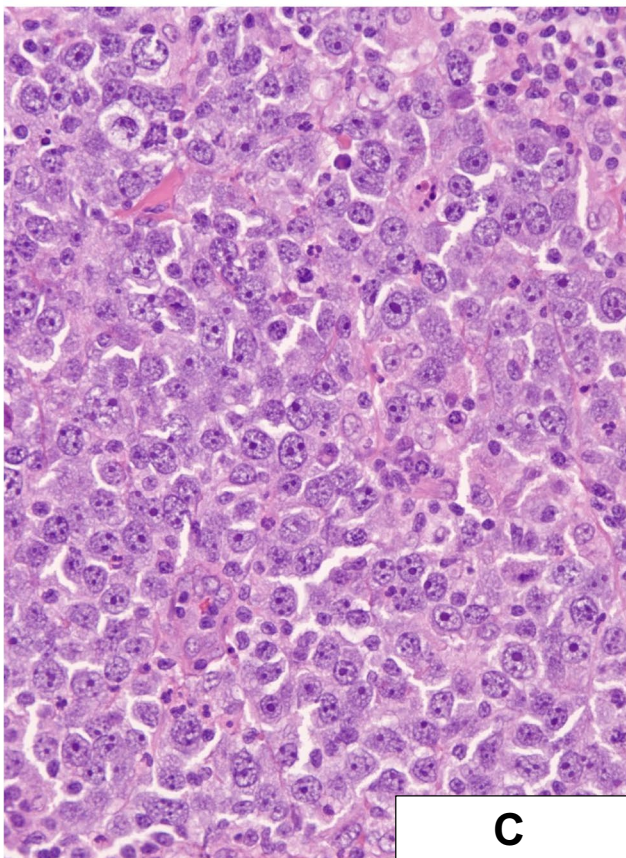
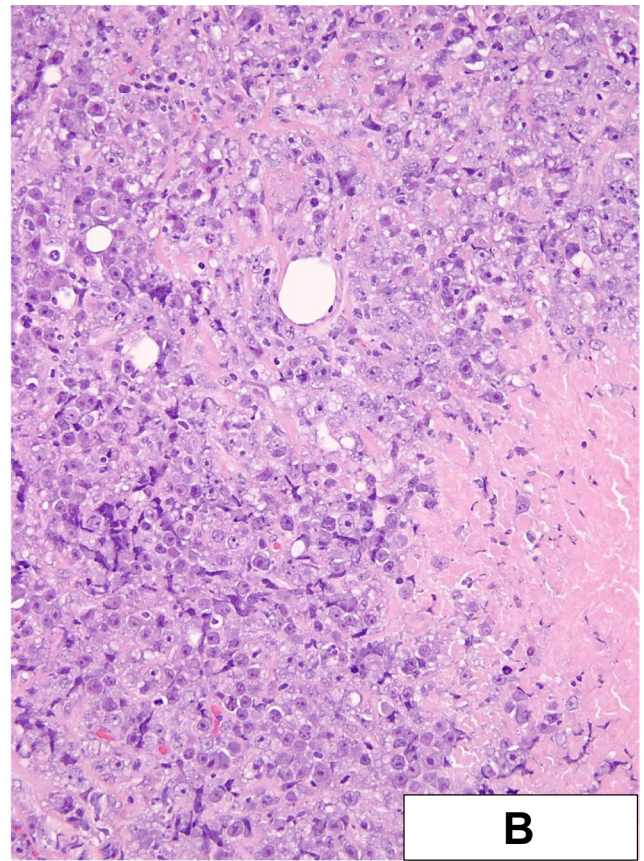
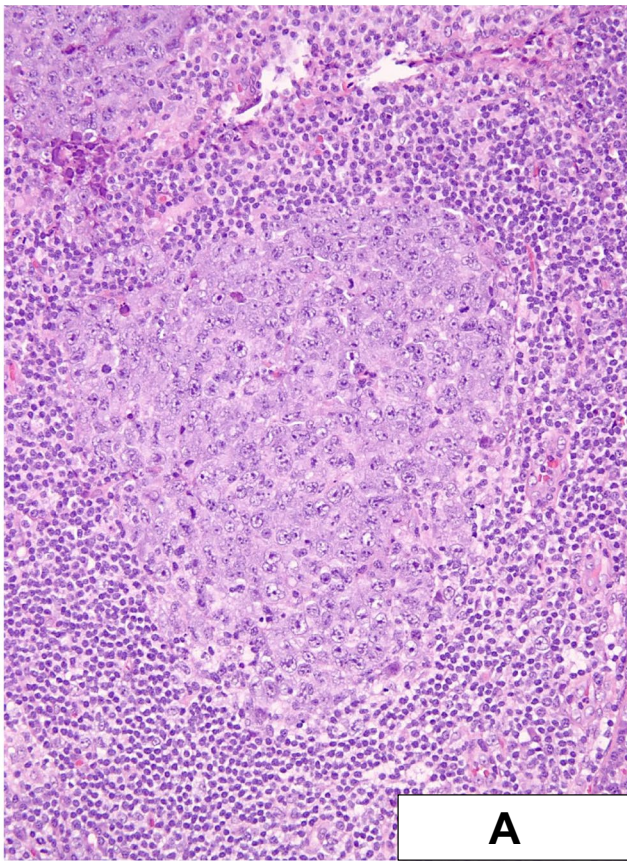
Introduction

Epstein-Barr (EBV)-positive follicular lymphoma (FL) is uncommon with a prevalence of 2.5 to 6% of follicular lymphomas [1] [2] [3]. While fewer than 30 cases have been previously reported, several common features have emerged. Typically, EBV-positive FL is of histologic grade 3 and/or commonly progresses to higher-grade FL or diffuse large B-cell lymphoma (DLBCL) [3] [4]. Secondly, in contrast to other EBV-associated lymphomas, many patients with EBV-positive FL are immunocompetent.

In this report, we describe a case of EBV-positive FL and concurrent EBV-negative DLBCL. Considering shared molecular genetic abnormalities, DLBCL is most likely clonally related to FL and this case illustrates branched evolution model which has been reported in the majority of

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◀**Fig. 1** Histologic and cytomorphic features of follicular and diffuse components. **A.** Neoplastic follicles, H&E 200x. **B.** Diffuse area with focal necrosis, H&E 200x. **C.** Neoplastic follicles were composed of large atypical lymphoid cells with abundant cytoplasm, round to oval vesicular nuclei and prominent nucleoli, H&E 400x. **D.** Similar cytomorphic features were seen in diffuse areas, H&E 400x

FL [5]. In contrast to some other EBV-positive lymphoproliferations [6], this case was characterized by an indolent clinical course.

Clinical history

The patient is a 58 year-old Caucasian male with a history of mixed connective tissue disease diagnosed in 1992. In the past, the patient was treated with steroids and methotrexate, and currently has only been receiving hydroxychloroquine. The patient presented with extensive right axillary and subpectoral lymphadenopathy. He reported fevers but denied weight loss or night sweats. A PET/CT scan showed bulky, highly FDG-avid axillary lymphadenopathy. A core needle biopsy revealed focal proliferation of large atypical lymphoid cells positive for EBV and was considered not sufficient for a definitive diagnosis. Subsequently, a lymph node excision was performed and a diagnosis of EBV-positive FL (grade 3B) transforming to DLBCL was rendered. The patient was treated with six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) with involved-field radiotherapy and remains in complete remission since 2016.

Material and methods

Formalin-fixed and paraffin-embedded tissue (FFPE) was used for hematoxylin and eosin stain, immunohistochemistry (IHC), and in situ hybridization (ISH). IHC was performed using antibodies against CD20, PAX5, BCL6, CD10, HGAL, LMO2, BCL2, CD30, MYC, CD21, CD23, CD35, MUM1, kappa, and lambda light chain. EBV was detected by EBER 1 DNP Ventana ISH probe against EBV-encoded small RNAs (EBER). The IHC and EBV ISH were performed in the clinical diagnostic laboratory of Indiana University Health according to the previously described procedures. EBV nuclear antigen 1 (EBNA1) IHC was performed as previously described at the University of Wisconsin Madison [7]. Fluorescence in situ hybridization analysis for *MYC*, *BCL2*, and *BCL6* rearrangements (Abbott Molecular, Abbott Park, IL) was performed at the Mayo Clinic (Rochester, MN) as previously described [8].

Next-generation sequencing (NGS) was performed separately for FL and DLBCL components at Indiana University

Health. DNA and RNA sequencing included 453 genes involved in lymphomas, relevant viruses, and dominant immunoglobulin (IG) heavy chain usage. The average coverage was 334X and 240X for follicular and diffuse components, respectively. In addition, B-cell clonality was examined by PCR with BIOMED-2 immunoglobulin heavy chain (IgH) clonality assay using micro-dissected FFPE tissue from FL and DLBCL as previously described [9].

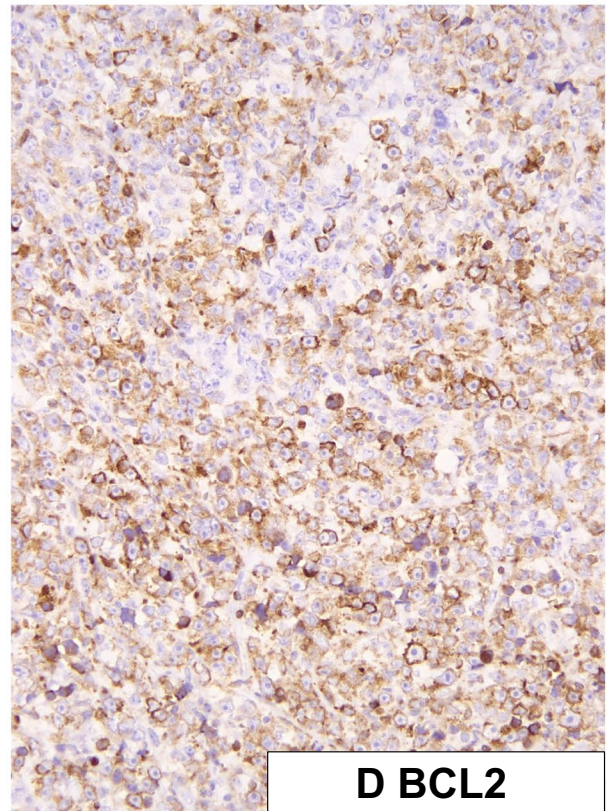
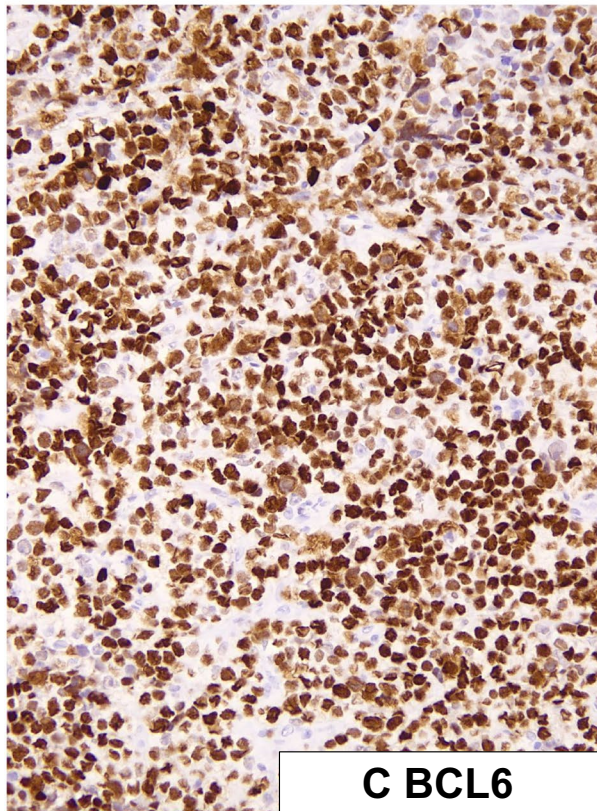
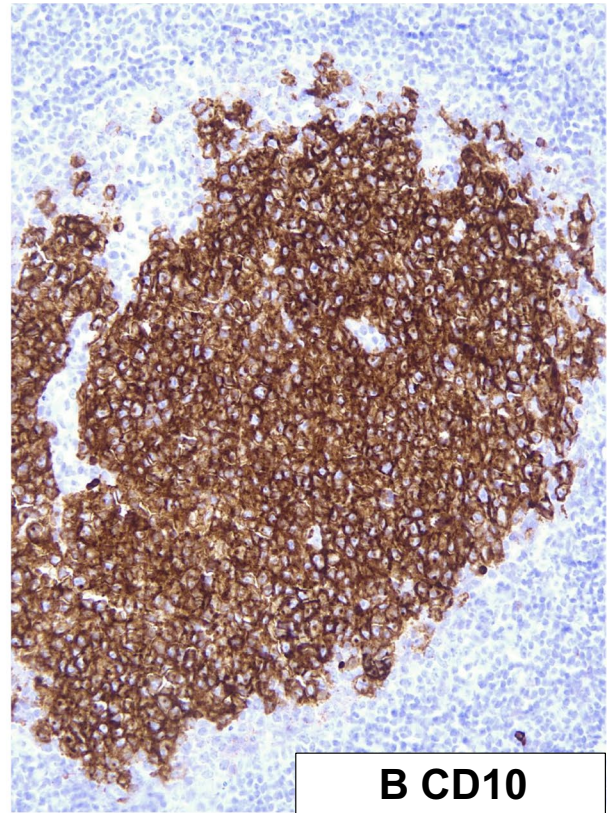
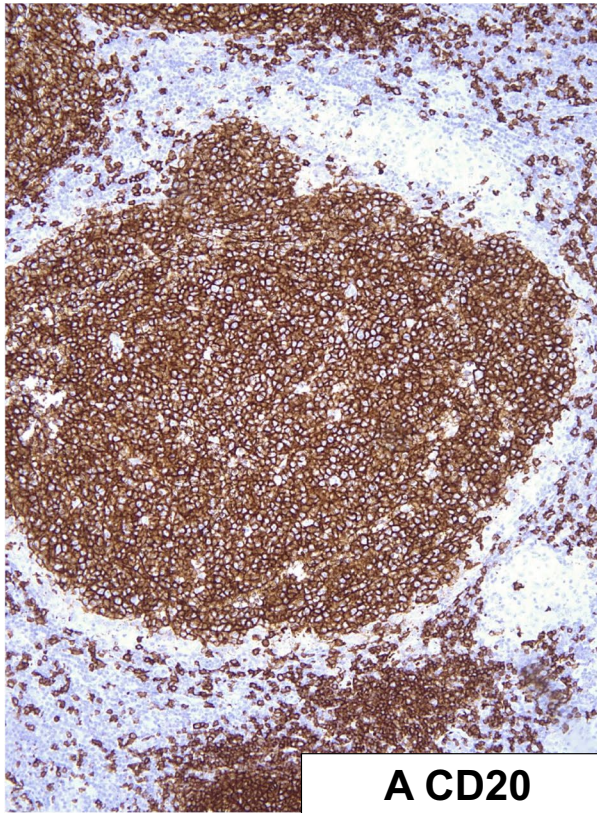
Results

Histologic sections showed lymph nodes with architecture almost entirely effaced by a nodular and diffuse proliferation of large, atypical lymphoid cells with moderately abundant cytoplasm, round to oval vesicular nuclei, and prominent multiple or single nucleoli consistent with centroblasts and immunoblasts (Fig. 1. A–D). Diffuse areas included prominent necrosis and extended into perinodal soft tissues. Neoplastic follicles were scattered about and were also present in areas with partially preserved nodal architecture including secondary follicles, paracortical expansion, and plasmacytosis. In addition, extensive granulomata composed of epithelioid histiocytes and giant cells were seen surrounding neoplastic follicles and were also scattered throughout lymph nodes.

The lymphoid cells in neoplastic follicles were positive for CD20, PAX5, BCL6, CD10, HGAL, and MYC (Fig. 2 A, B, E), and negative for LMO2 and MUM1. The BCL2 expression in neoplastic follicles was focal and weak. The reactive residual follicles were positive for CD20, PAX5, CD10, BCL6, LMO2, and HGAL. Immunostains for CD21, CD35, and CD23 showed prominent follicular dendritic cell meshworks in neoplastic follicles and were absent in areas transitioning to a diffuse pattern (Fig. 2 G). Neoplastic cells in diffuse areas were positive for CD20, PAX5, CD10, BCL6, BCL2, and MYC, weakly positive for HGAL and negative for LMO2 and MUM1 (Fig. 2 C, D, F). CD30 immunostain was negative in both follicular and diffuse areas. Kappa and lambda light chain immunostains were negative in neoplastic lymphoid cells and showed a polyclonal pattern of expression in plasma cells.

Neoplastic follicles were positive for EBV ISH in more than 80% of nuclei, whereas diffuse areas were negative for EBV (Fig. 2 H, I). Neoplastic follicles and diffuse areas were negative for EBNA1 and LMP1. EBV status was confirmed by NGS, which showed a presence of EBV in follicular component and DLBCL negative for EBV.

We also performed FISH studies for *BCL2*, *BCL6*, and *MYC* rearrangements. *MYC* break-apart probe (BAP) and *MYC/IGH* dual-color dual-fusion (D-FISH) probes sets identified a *MYC/IGH* rearrangement in 95–100% of interphase nuclei in both follicular and diffuse areas (Fig. 2 J, K).



◀ **Fig. 2** Immunohistochemical stains, EBER in situ hybridization and fluorescence in situ hybridization. **A.** CD20 immunostain in neoplastic follicles. **B.** CD10 immunostain in neoplastic follicles. **C.** BCL6 immunostain in diffuse area. **D.** BCL2 in diffuse component. MYC immunostain in follicular (**E**) and diffuse area (**F**). **G.** CD21 immunohistochemical stain highlights follicular dendritic cell meshwork in the neoplastic follicle. EBER in situ hybridization was positive in neoplastic follicles (**H**) and negative in diffuse areas (**I**). **J.** MYC break-apart FISH probe was positive (arrows) in follicular and diffuse areas. **K.** Fluorescence in situ hybridization using a MYC/IGH dual-color dual-fusion probe set demonstrated MYC/IGH rearrangement (arrows) in follicular and diffuse areas. **L.** BCL6 probe demonstrated a BCL6 rearrangement (arrow) in neoplastic lymphoid cells only in follicular areas

In addition, BCL6 (BAP) probe showed 58% of interphase nuclei with BCL6 rearrangement in follicular areas (Fig. 2 L), whereas it was negative in diffuse areas. Lastly, BCL2 BAP studies showed no rearrangement in follicular or diffuse areas, despite significant BCL2 expression as seen on immunohistochemistry in diffuse areas.

Three and 9 somatic mutations were identified in FL and DLBCL, respectively. The FL component showed the following mutations: ATM (V410A, variant allele frequency (VAF) 62%), DDX3X (Y243X, VAF 18%), and RAC1 (A159V, VAF 2%). The DDX3X mutation was designated as likely oncogenic due to the loss-of-function mechanism. The variants identified in DLBCL component included DDX3X (Y243X, VAF 62%), TP53 (R175H, VAF 66%), MYC (S21T, VAF 37%), KLHL6 (L58P, VAF 37%), RHOA (A61D, VAF 46%), APC (Q1444X, VAF 3%), KRAS (G60S, VAF 3%), NF1 (R2258X, VAF 3%), and NUP93 (Q15X, VAF 5%). DEAD-Box Helicase 3 X-Linked (DDX3X) Y243X was the only variant shared by FL and DLBCL and its VAF increased from 18 in FL to 62% in DLBCL component, respectively.

Heavy chain usage was determined separately for follicular and diffuse component and showed IGHV2-26, IGHD1-14, and IGHJ4 in FL, and IGHV3-43, IGHD6-13, and IGHJ4 in DLBCL. We also performed PCR with Biomed-2 primers on microdissected FL and DLBCL components. DLBCL showed 331 bp product in FR1 primer, and 248 bp and 266 bp products in FR2 primer. FL showed a polyclonal pattern in all three primer sets.

Discussion

EBV-associated lymphoproliferative disorders are a heterogeneous group of diseases including indolent conditions and highly aggressive lymphomas with variable presence of EBV and diverse latency types [6]. EBV-positive FL is not well

characterized due to its low prevalence ranging from 2.5 to 6% of FL [1] [2] [3]. Nevertheless, it is known that the

majority of cases are of histologic grade 3 and/or show progression to high-grade lymphoma. Mackrides et al. reported the two largest series (10 and 12 cases, respectively) of EBV-positive FL and identified several cases, which progressed to DLBCL or higher-grade FL within 1 to 6 years, although detailed pre- and post-transformation EBV data were not available in the majority of cases [3] (Table 1). EBV-positive FL is usually of latency type II [3] [2]. In the current case, the follicular areas were positive for EBER, and negative for EBNA1 and LMP1 by immunohistochemistry, indicating latency type 0. However, EBNA1 expression in type I or type II latency driven by viral promoter (qp) [10] [11] can be weak [12], and antibodies for EBNA1 may show poor sensitivity [13]. Therefore, we cannot exclude the possibility of type I latency in our case. This latency type has been rarely documented in EBV-positive FL [2] [3].

The IHC showed neoplastic follicles as well as diffuse areas to be positive for CD10, BCL6, and HGAL but negative for LMO2 and MUM1, which is consistent with germinal center cell phenotype [14] [15]. Of note, loss of LMO2 expression in germinal center cell-derived lymphomas was previously reported in lymphomas with MYC rearrangement [3, 16]. The BCL2 rearrangement was not detected in this case, despite significant BCL2 expression seen by IHC primarily in diffuse areas. The expression of BCL2 in neoplastic follicles was focal. Previously, Mackrides et al. reported a case of EBV-positive FL with BCL2 protein expression without a BCL2 rearrangement [3]. In BCL2/IGH-negative FL, mechanisms of BCL2 overexpression are largely unknown except for a few previously reported cases with BCL2 locus amplification and trisomy 18 [17, 18]. Although there are differences in gene expression and genetic alterations between BCL2 rearrangement-negative and -positive FL, prognosis and survival do not differ [17] [19] [20] [21].

Similar to the patient described in this report, Mackrides et al. reported a case of EBV-positive BCL2 rearrangement-negative FL with a history of hydroxychloroquine treatment (Table 1) [3]. Although the correlation between medication history and pathophysiology of BCL2 rearrangement-negative EBV-positive FL has not been explored, rare cases of iatrogenic immunodeficiency-associated lymphoproliferative disorders have been reported in association with hydroxychloroquine, and therefore, this case may be considered iatrogenic immunodeficiency-associated disorder [22] [23]. Hydroxychloroquine is an immunomodulatory drug used to treat malaria and autoimmune diseases [24]. It has been shown to reduce TNF alpha and IFN alpha production in plasmacytoid dendritic cells upon Toll-like receptor 9 stimulation and to decrease TNF alpha and IL-6 production in B-cells [25] [26]. Interestingly, chloroquine, which hydroxychloroquine is derived from, reportedly causes phosphorylation of KAP1 through ATM, leading to reactivation of EBV lytic replication [27]. Murata et al.

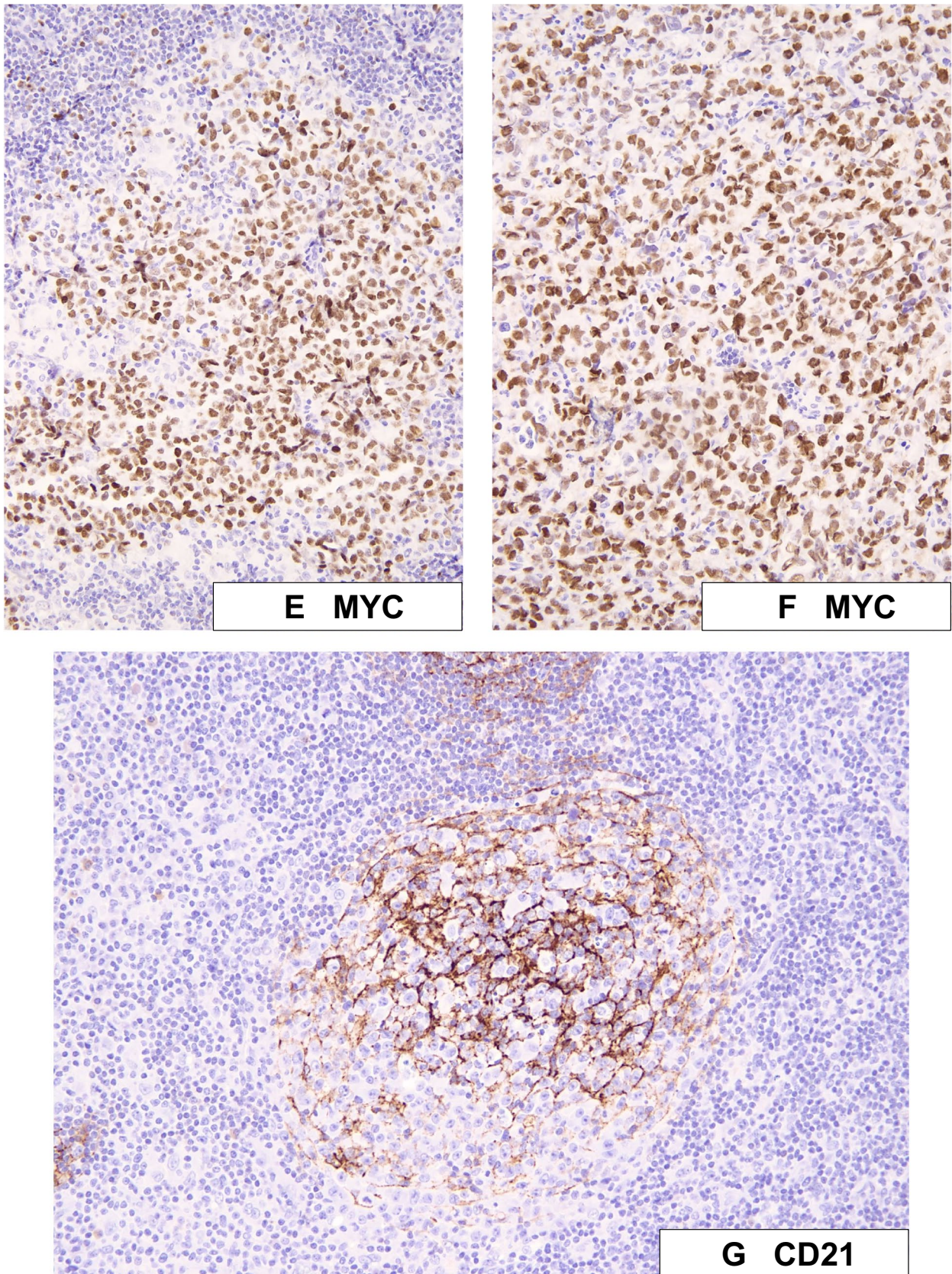


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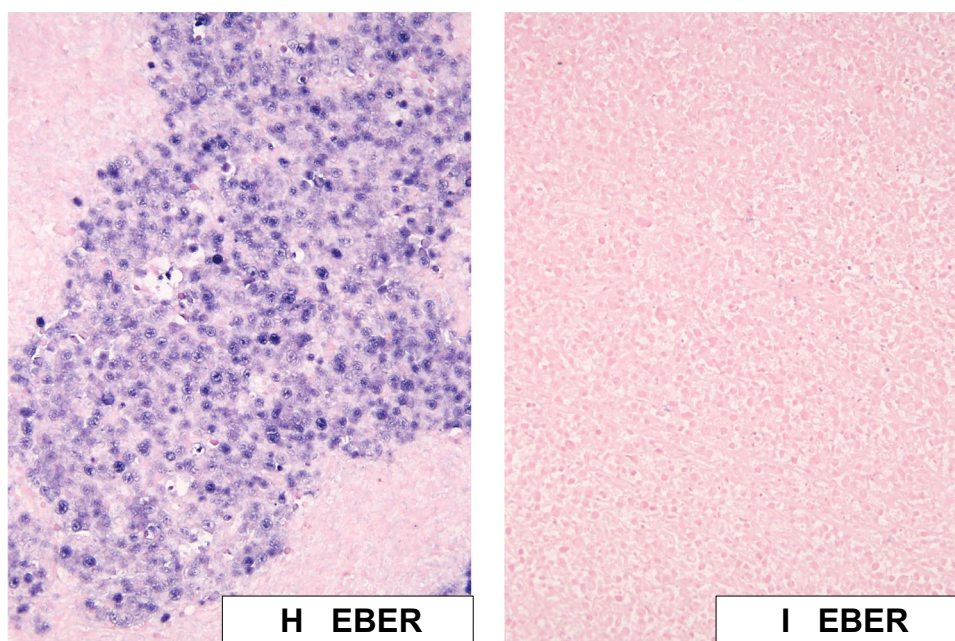


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suggested that EBV-infected cells in lytic cycle reactivation might experience genomic instability through activation of recombination or repair genes, and therefore, we speculate that hydroxychloroquine might introduce genomic instability and promote growth in EBV-positive germinal center cells [28] [29].

Constitutive *MYC* expression has also been shown to induce genomic instability in vitro and in vivo [30]. *MYC* gene rearrangement can be found in 8–38% of FL at the time of transformation [5, 31] [32]. When *MYC* rearrangement is observed in low-grade FL cases with *BCL2* rearrangement, it may be associated with an aggressive disease course [32]. However, Yoshida et al. reported a case of FL without *BCL2/IGH* translocation with *MYC* rearrangement and with an indolent clinical course [33]. In the current report, *BCL2* *BAP* FISH was negative in follicular and diffuse areas, and both follicular and diffuse areas showed *MYC/IGH* rearrangement. The patient responded well to chemotherapy and radiation, and remains in complete remission.

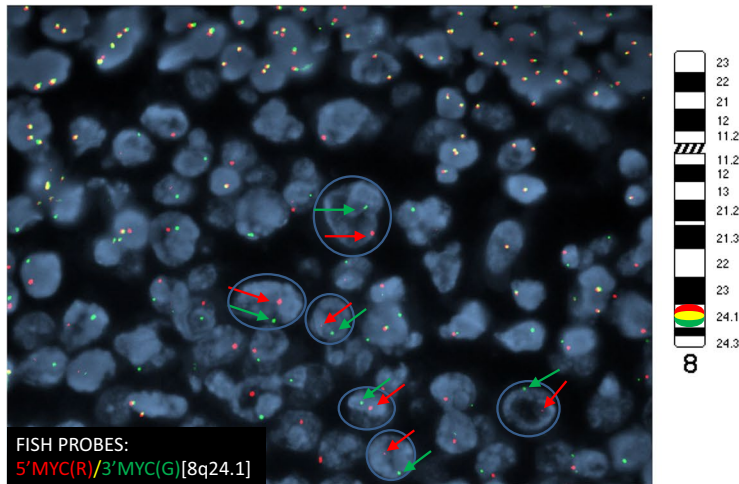
The prevalence of *MYC/IGH* rearrangement in EBV-associated B-cell lymphoproliferative disorders is variable. The highest frequency of *MYC* rearrangement is observed in Burkitt lymphoma and EBV-positive plasmablastic lymphoma, 80–90% and 74% of cases, respectively [6] [34] [35]. Both entities show EBV latency type I, similar to the reported case [6].

Next-generation sequencing provided further insights into the pathogenesis of the reported case. Mutations typically found in EBV-negative FL were not seen. Instead, the follicular component harbored mutations in *ATM*, *DDX3X*,

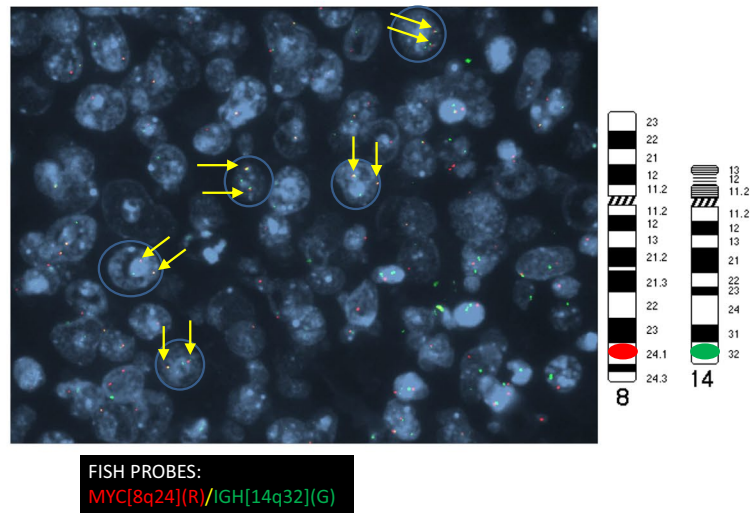
and *RAC1* genes. *ATM* is a master regulator of cell cycle checkpoint signaling pathways required for a response to DNA damage and maintaining genome stability. In small cell lymphoma, *ATM* mutations are frequent in mantle cell lymphomas and are not common in FL. In addition, even in mantle cell lymphoma cases, *ATM* mutation does not affect patients' prognosis [36], suggesting that *ATM* mutation might not have impact on tumor progression and eventually *ATM*-positive clones may disappear during clonal evolution. *DDX3X* is the fourth most commonly mutated gene in Burkitt lymphoma and is considered to be a driver mutation in EBV-positive lymphomas [37, 38]. Moreover, a loss of function *DDX3X* mutations is enriched in *MYC*-rearranged DLBCL with functional cooperation between mutated *DDX3X* and *MYC* [39]. Not surprisingly, in addition to shared *DDX3X* mutation and *MYC/IGH* rearrangement, DLBCL show a number of private mutations affecting DNA damage response, cell cycle progression, B-cell receptor signaling, and apoptosis. Mutations of *TP53*, *MYC*, *KLHL6*, and *RHOA* genes were found to have the highest VAF, whereas other mutations represented minor variants. Such intratumoral heterogeneity has been previously described in transformed FL [40].

The presence of shared genetic abnormalities and private mutations supports a branched evolution model previously reported for the majority of transformed FL cases (Fig. 3) [5]. It is conceivable that EBV infection/reactivation was an initiating event and occurred in the context of hydroxychloroquine immunomodulation [41] [4] [42]. Since FL and DLBCL components harbored *DDX3X* mutation and *MYC/*

J. Break-Apart MYC probe



K. Dual Color Double Fusion (DFISH) for MYC/IGH fusion



L. BCL6 FISH

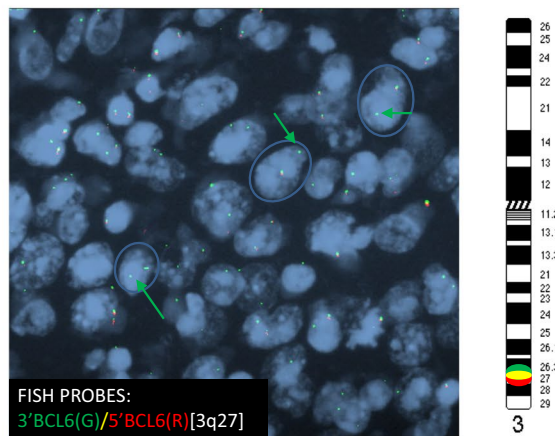
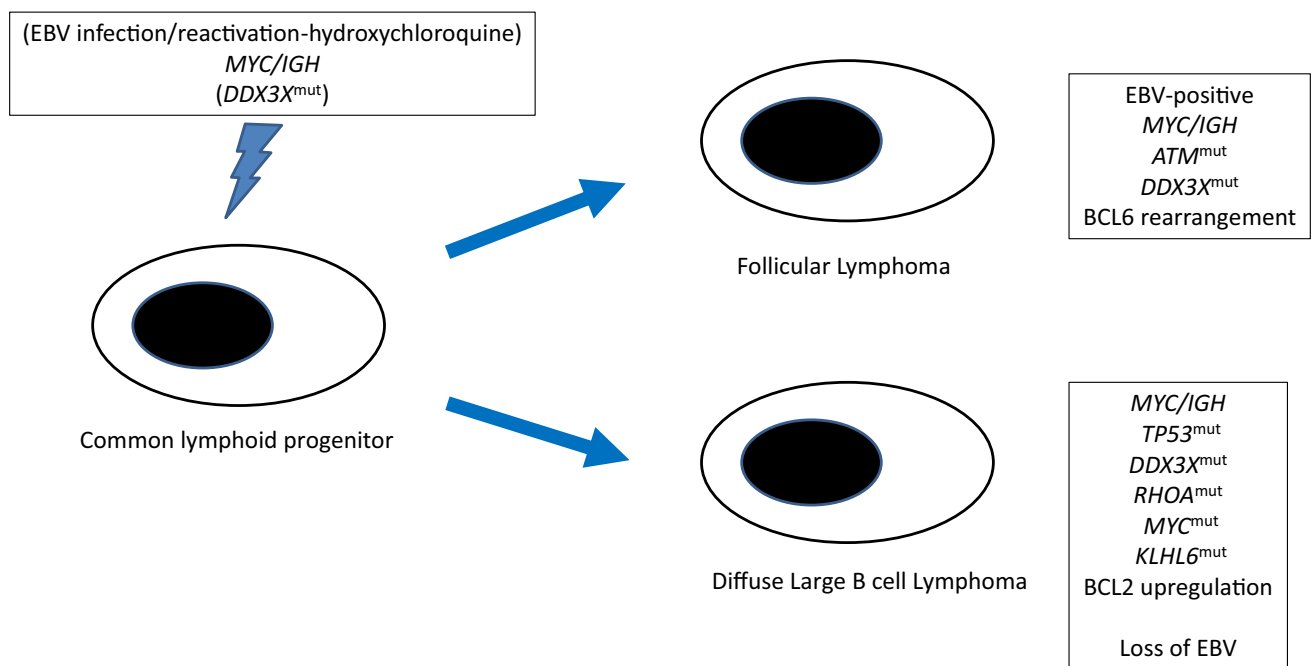


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Table 1 EBV-positive follicular lymphoma cases with progression and transformation reported in the literature

Reference	Age	Location	Immunosuppression	Grade at initial diagnosis	EBER	EBNA1	LMP1	Time to progression (years)	Diagnosis at progression
Current case	58	Axilla subpectoral	Hydroxychloroquine	3B	+	-	-	Concurrent	Concurrent DLBCL
Granai et al	73	Multiple	Chemotherapy	2	+	+	-	6	DLBCL
Mackrides et al	83	Cervical	None	3A	+	NA	NA	3.8	DLBCL
	48	Inguinal	None	1–2	+	NA	+	7.2	DLBCL
	31	Mediastinum	None	3A	+	NA	-	<1	DLBCL
	33	Supraclavicular	None	3A	+	NA	+	5.6	DLBCL
	64	Spleen/multiple	None	3A	+	NA	+	1.1	DLBCL
	76	Abdomen	Hydroxychloroquine	1–2	+	NA	NA	6.1	FL 3A
	33	Cervical	None	1–2	+	NA	+	4.3	FL 3A

**Fig. 3** Proposed branched evolution in the reported case of EBV-positive FL and concurrent EBV-negative DLBCL based on contributions of *MYC*, EBV, and shared and unique mutations to lymphomagenesis.

EBV infection/reactivation and *DDX3X* mutation are shown in parenthesis at the level of common lymphoid progenitor as it is also plausible that these events occurred later in the evolution of the disease

IGH rearrangement, it is plausible that the EBV-infected common progenitor acquired *DDX3X* mutation and *MYC/IGH* as initial steps in lymphomagenesis [40]. In addition, DLBCL acquired numerous mutations promoting tumor growth and at this point EBV became dispensable, which would explain a loss of EBV in diffuse areas consistent with “hit-and-run” hypothesis [43] [44]. The unique *IGH* VDJ usage seen in FL and DLBCL is unusual and may represent two distinct amplified alleles. As an alternative, *DDX3X* mutations could have occurred later in the development of FL and DLBCL, and/or EBV infection/reactivation occurred independently as well, only in the FL branch.

Interestingly, recent phylogenetic analysis of B-cell receptor subclones in FL at single cell level demonstrated clonal heterogeneity in a subset of FL cases [45]. Such single-cell sequencing, if feasible, would have allowed for further clarification of clonal evolution and the role of individual mutations in our case.

In summary, we describe a case of EBV-positive FL and concurrent EBV-negative DLBCL. We speculate that hydroxychloroquine-induced immunomodulation may have led to EBV infection/reactivation as an initiating event. The presence of molecular genetic abnormalities shared by FL and DLBCL point to a common progenitor. The presence

of mutations unique to FL and DLBCL and distinctive IGH usage support the branched clonal evolution model.

Declarations

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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