



A Case Report of Classic Hodgkin Lymphoma with Unusually Abundant Tumor Cell Expression of B-Cell Markers: A Diagnostic Dilemma and Treatment Challenge

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Background

The diagnosis of classic Hodgkin Lymphoma (cHL) appears quite straightforward, as it is built upon extended histological and immunophenotypic assessment. Hodgkin and Reed-Sternberg cells reflect monoclonal cell proliferation, presumably originating from germinal center B-cell at the centroblast stage. In addition, HL is characterized by unique microenvironment, which often plays the crucial role in establishing accurate diagnosis. In general, malignant cells lose the B-cell phenotype, Yet, one third of cHL cases express at least one B-cell marker such as: **CD19, CD20, CD79a, bcl-6, CD138, PAX5 and MUM1**, which in some instances leads to diagnostic difficulties in distinguishing cHL from B-cell Lymphomas. In line with reported data, classical B-cell marker CD20 is expressed on Hodgkin-cells even up to 80% in some cases, but typically the stain appears to be weaker in comparison to reactive normal B-cells.¹

The association of cHL with Epstein- Barr Virus (EBV) is well known and EBV infection occurs in even up to 40% of cases. Recent molecular studies show that EBV may affect the cellular microenvironment, in particular B-cells by expressing LMP1 and LMP2A, which may mimic key signals of their growth and survival. Yet, the exact pathophysiological mechanism remains unelucidated^{2, 3}.

Objective

Our goal is to present a diagnostically complex case of **cHL CD30+/CD15+** in a 21-year-old boy. What makes this case specific is the imunohistochemical staining which demonstrated unusual, strong expression of markers of B-cell differentiation and positivity for Epsten-Barr Virus (EBV). These findings brought out serious constrains in the differential diagnosis of an EBV positive diffuse large B-cell Lymphoma.

Even more, we had different histological findings from 3 institutions, as discussed in following sections.

Case report – initial presentation

Medical history and physical examination: A previously healthy 21-year –old boy presented at our institution with bilateral **neck lymphadenopathy in lower cervical parts (up to d=3x3cm)**. These lymph nodes were fixed, painless and of hard consistency. On clinical examination, he had no lymphadenopathy in other regions nor organomegaly.

He experienced no B-symptoms.

His past and recent medical history as well as family history were unremekable.

Laboratory tests: Except for **slightly elevated sedimentation rate (30/-)**, blood and biochemistry analyses were within normal ranges.

Diagnostic ambiguity – three histopatological interpretations

Fine needle aspiration of the cervical lymph node was performed, supporting the diagnosis of malignancy – **class V** and it was suggestive of Hodgkin Lymphoma.

#1 Histopathology Report – Inistitut of Pathology – Skopje, Republic of North Macedonia / Onkoloshki Institut Ljubljana – Oddelek a patologijo – EBV associated B-cell Lymhoma

The enlarged lymph node was surgically extirpated. **Histological examination** of the surgically extirpated cervical lymph node was puzzling. HE and Giemsa- staining showed tumor cell morphology resembling unclassified large cell B-cell lymphoma and classical Hodgkin Lymphoma (PTLD-like neoplasm?)

Immunohistochemistry: The atypical lymphoid cells expressed classical Hodgkin phenotype CD30+/CD15+, but they showed strong CD20+ co-expression (figure 1-5) . The ki-67 proliferation index was positive in 80-90%. The tumor cells were **strongly positive for EBV** and a diagnosis of EBV-associated B-cell Lymphoma was assumed (figure 6). Additional immunohistochemical staining were performed at *Onkoloshki Instiut - Ljubljana*. Tumor cells were positive for CD15, CD30, CD20, EBV and also for MUM-1, PAX-5 aand PDL1.

PCR studies were negative for B and T-cell rearrangement.

Additionally, **FISH analyses for MYC gene rearrangement was performed and it was negative** (figure 7).

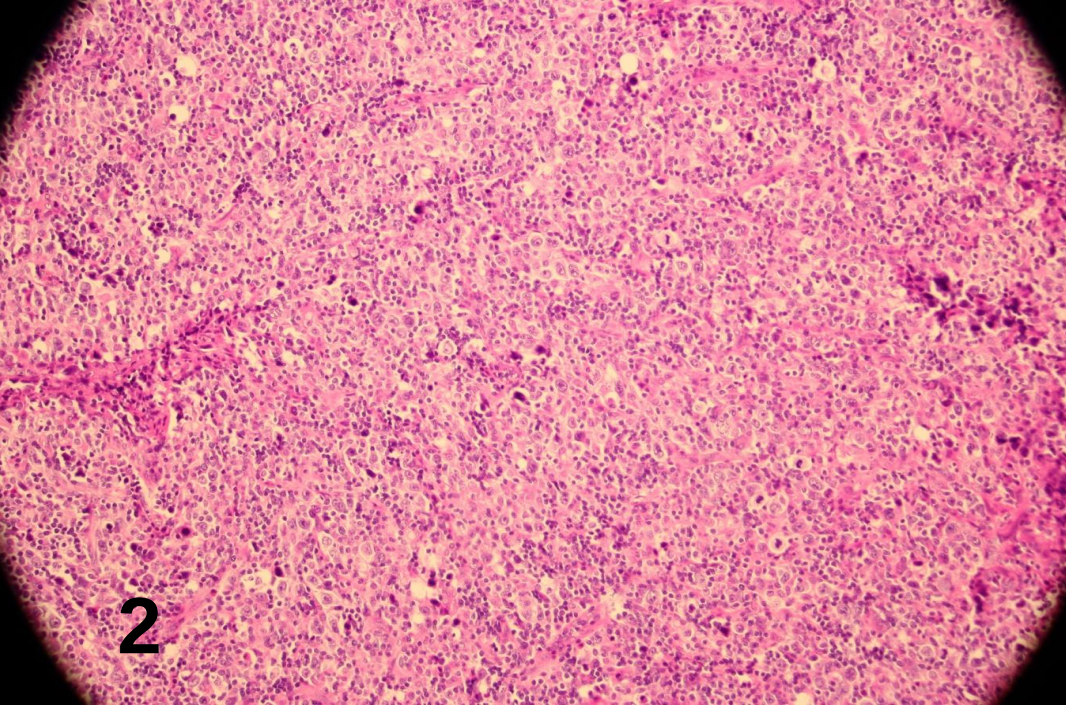
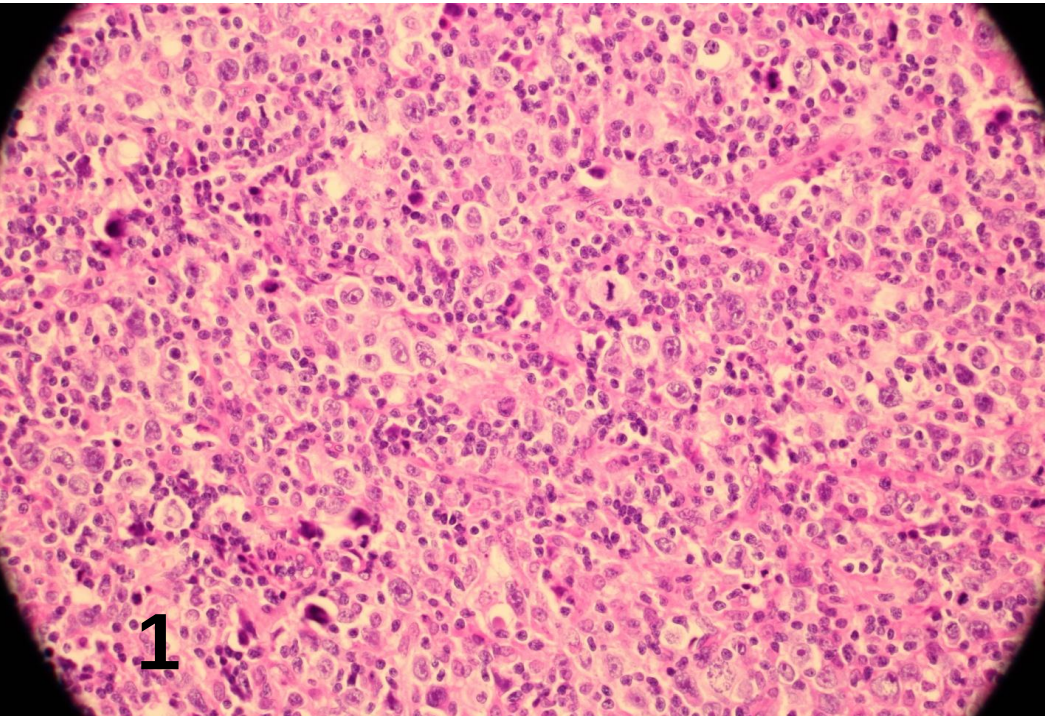


Figure 1 and 2 - HE staining showing nodular infiltration by pleomorphic lymphoma with large atypical cells with eccentric irregular nuclei and scant cytoplasm, resembling Hodgkin cells, but also sporadic Reed- Sternberg cells.

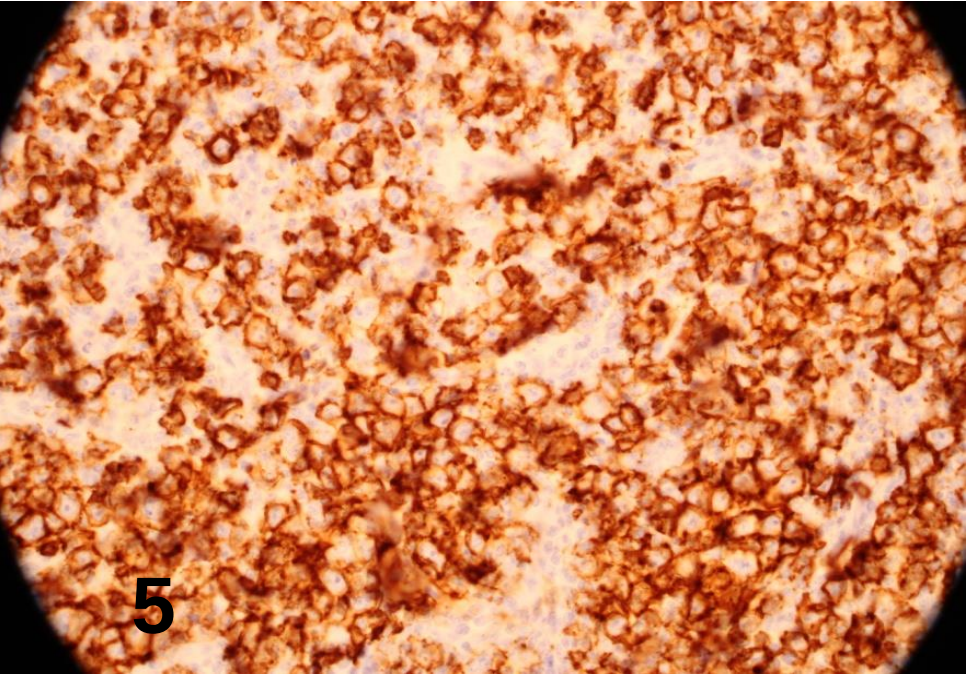


Figure 5 –Imunostaining for CD20

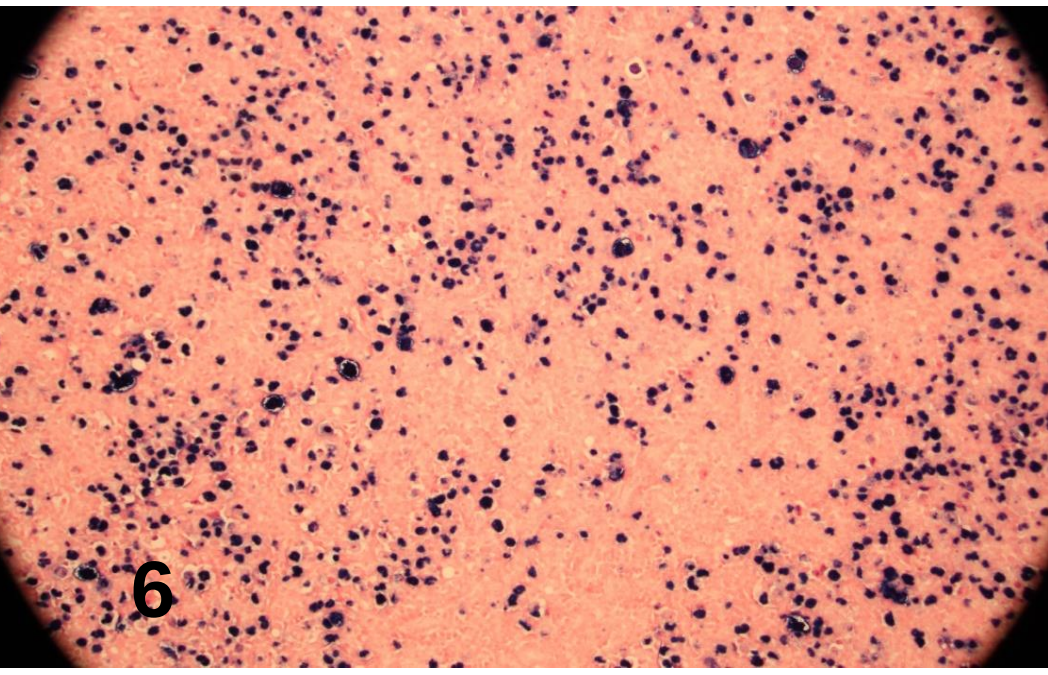


Figure 6 – Immunostaining for EBV

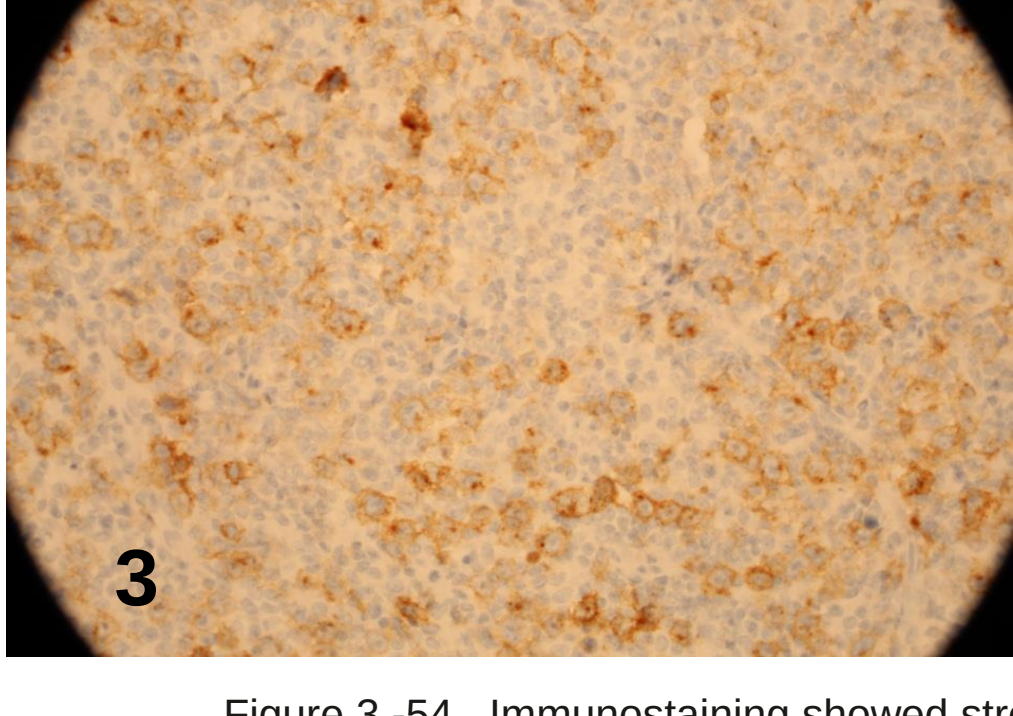


Figure 3 -54– Immunostaining showed strong positivity for CD30 (3), partially for CD15 (4)

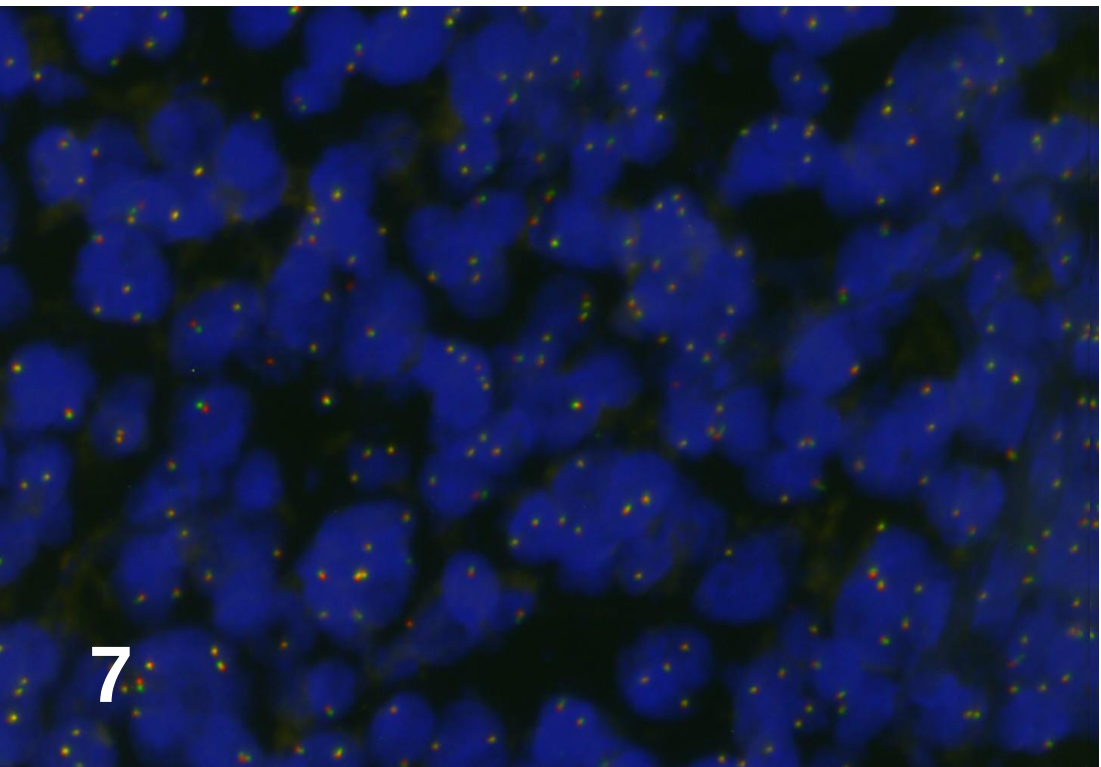
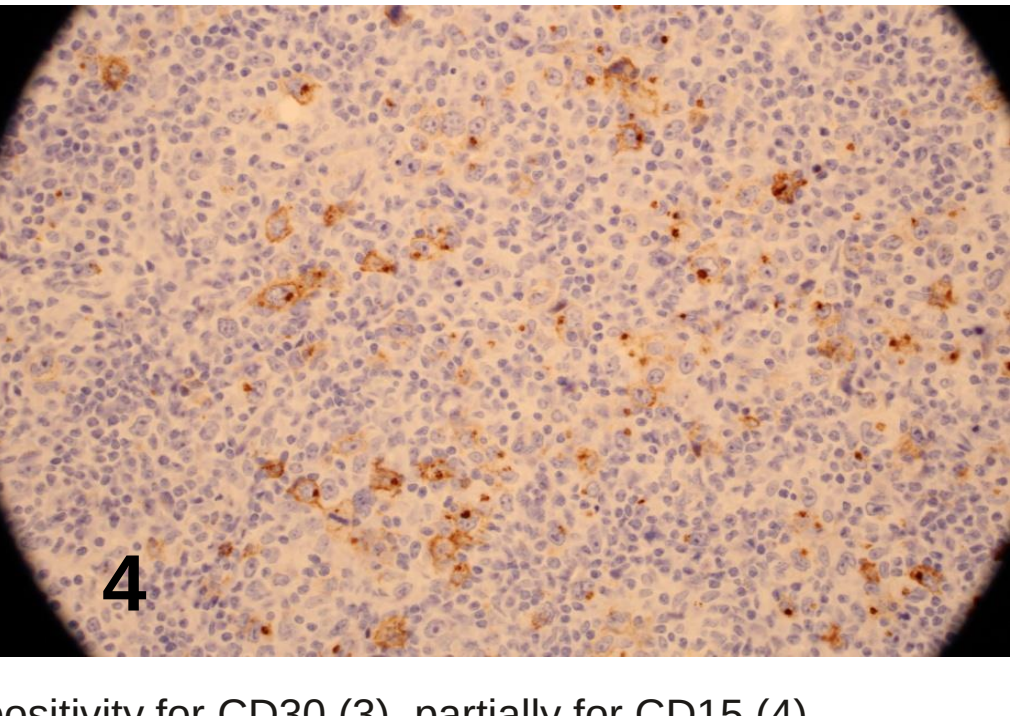


Figure 7 – FISH analyses for MYC translocation t(8,v)(q24:v) – negative

#2 Histopathology Report – Referenzzentrum Lymhome der SAKK – Basel - classical Hodgkin Lymphoma CD20+

Lymphoma formations were strongly positive for CD30, CD15 and Epstein Barr virus and for EBV receptor CD21, attenuated positive for PAX5 and unusually positive for BCL-6, strongly positive for CD20 and MUM1 (figure 1-6)

In the additional staining performed, these cells were negative for CD45, CD791, BOB1 and MEF2B. Therefore, in the absence of sufficient diagnostic criteria for EBV positive diffuse large B-cell lymphoma, the diagnosis of classic Hodgkin Lymphoma with unusually abundant tumor cells was favored.

#3 Histopathology Report – National Institutes of Health/ National Cancer Institute – EBV positive T-cell/hystoycite rich large cell B-cell lymphoma

The large atypical lymphoma cells were positive for CD20, CD79a (weak), CD30 and PDL-1, but negative for CD15, IgD and LMP1. CD3 highlights numerous background T-cells, which are negative for PD1. EBER was positive in the atypical cells.

Molecular studies for B-cell rearrangement and next generation sequencing were performed and were negative.

Initial PET/CT staging

Initial **PET-CT scan** was assessed as **stage IIA** disease, involving supradiaphragmatic lymph nodes: cervical lymph nodes (SUVmax=15,9; d=25mm) and mediastinal lymph nodes levels 2R/L, 3, 4 R/L, 5 and 6 (SUVmax= 17,1; d=30mm). Initial PET/CT findings compared to interim PET/CT are shown on figure8.

Treatment and outcome

•In consensus with reported literature and in consultation with reference centre, treatment was initiated with R-ABVD regimen. Rituximab was administered once weekly in the first cycle (D1, D8, D15, D21) and on D1 and D15 from the seconc cycle on.

•Interim PET/CT scan was performed after completing second cycle cchemotherapy. It was assessed as Deauville score 2.

Complere response was achieved with FDG-uptake in lymph nodes with maximal diametar to 10mm < mediastinum FDG-uptake.

Therefore, treatment was continuied with additional 2 cycles R-ABVD. Involved field radiotherapy is planned after chemotherapy termination.



Figure 8a, 8b, 8c – CT and PET-WB
Initial PET/CT scan on the left side, compared to
interim PET/CT findings on the right side.

References:

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3. Santos MAO, Lima MM. CD20 role in pathophysiology of Hodgkin's disease. Rev Assoc Med Bras (1992). 2017