

Hodgkin Variant of Richter's Transformation in Chronic Lymphocytic Leukemia (CLL): An Illustrative Case Report and Literature Review

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ABSTRACT

Hodgkin lymphoma variant of Richter's transformation (HL-RT) is a rare event, occurring in < 1% chronic lymphocytic leukemia (CLL) cases, of which, in < 10% cases, HL is the first finding leading to a diagnosis of CLL that co-exists simultaneously. Here we report a 60 years old male patient who presented with an outside diagnosis of lymphocyte-rich classical HL. On evaluation, he had only B-symptoms in the form of low-grade fever and weight loss. Peripheral smear revealed mild leukocytosis with an absolute lymphocytosis and a few smudge cells. Bone marrow (BM) aspirate and biopsy exhibited diffuse infiltration by a small cell, low grade, Non-Hodgkin's lymphoma with no immunohistochemical evidence of HL. Flow cytometry performed on BM was consistent with classical immunoprofile of CLL. Meanwhile the lymph node received for review revealed diffuse effacement of nodal architecture by small mature lymphocytes with immunoprofile of CLL expressing CD20, CD5, and CD23. Interspersed between these cells, were a few eosinophils along with classical Reed Sternberg cells, expressing CD30, MUM-1, CD15, and dim PAX-5, with a surrounding rosette of T-Cells highlighted by CD3 and PD-1 and negative for CD45, CD20, and EBV immunohistochemistry. Fluorodeoxyglucose positron emission tomography (FDG-PET) scan revealed hepatosplenomegaly with multiple supra/intra diaphragmatic lymph nodes. So, a final diagnosis of HL-RT in CLL was considered. The patient is currently doing well after the first cycle of ABVD chemotherapy.

HL-RT occurring in CLL is a rare event with heterogeneous clinical presentation, morphology, clonal origin, disease course, prognostic features, and survival.

Keywords: Hodgkin's lymphoma; Richter's transformation; Chronic lymphocytic leukemia (CLL); Epstein-Barr virus (EBV); Fluorodeoxyglucose positron emission tomography scan (FDG-PET); Adriamycin; ABVD

INTRODUCTION

Richter's transformation (RT) in Chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) occurs in ~2-8% of cases, most common being diffuse large B-Cell lymphoma (DLBCL), with only < 1% CLL cases exhibiting Hodgkin's lymphoma (HL) variant transformation¹. More so, amongst approximately 100 cases of

Hodgkin's transformation of CLL that have been reported in world literature till date, majority occur after a median interval of 3-4 years from initial diagnosis of CLL^{2,3}. Herein, we describe a case diagnosed elsewhere as lymphocyte rich classical Hodgkin lymphoma which turned out to be Hodgkin variant RT at presentation with simultaneous co-occurrence of an undiagnosed and untreated CLL.

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Case presentation

A 60-year-old male presented elsewhere with neck swelling of two months duration. Fine needle aspiration cytology (FNAC) from the palpable right cervical lymph node was suggestive of lymphoproliferative disorder and corresponding biopsy was labelled as lymphocyte rich classical HL. With this diagnosis, the patient came to our hospital for further management. On evaluation, while he was febrile (99.5°F) and gave history of weight loss, rest of the general physical examination was unremarkable with no palpable lymph nodes or organomegaly. Complete blood counts (CBC) revealed a total leukocyte count (TLC) of 11,540 cells/ul with an absolute lymphocyte count of 3,730/ul, hemoglobin of 12.7 g/dL and platelet count of 1,70,000/ul. With the outside diagnosis of the classical Hodgkin's lymphoma, for staging purpose, bone marrow aspiration (BMA) and biopsy (BMBx) along with whole body Fluorodeoxyglucose labelled positron emission tomography with computed tomography (FDG PET/CT) were performed and the lymph node biopsy done outside was received for review at our center. The peripheral smear showed absolute lymphocytosis with a few smudge cells (Figure 1A).

BMA and imprint smears revealed a hypercellular marrow with trilineage hematopoiesis and marked prominence of mature small lymphocytes, which constituted 45% of all nucleated cells (Figure 1B & Figure 1C). BMBx also revealed a hypercellular marrow showing diffuse infiltration by sheets of small lymphoid cells (Figure 1D & Figure 1E) with no immuno-morphologically identifiable Reed Sternberg (RS) cells or RS like cells on CD30 immunostaining (Figure 1F).

In view of lymphocytosis, flowcytometric immunophenotyping (FCM) was performed on bone marrow, which revealed a lambda restricted B-cell non-Hodgkin's lymphoma (NHL) with immunoprofile of CLL expressing CD19 along with dim CD5, CD23 and CD20 and moderately bright CD200, CD79b and CD43. These cells were negative for surface kappa light chains, CD38, CD10, T-cell markers (CD3, CD4,

CD8) and hairy cell markers CD11c, CD103 and CD123 (Figure 2). PET/CT scan revealed hepatomegaly (craniocaudal extent of 16.5 cm) and splenomegaly (craniocaudal extent of 14.5 cm) with multiple metabolically active supra-diaphragmatic and infra-diaphragmatic lymph nodes (1.1 – 4.3 cm in size; SUV_{max} 1.7 -4.6).

The cervical lymph node biopsy on review (Figure 3) showed complete effacement of the lymph node architecture by an infiltrate composed of small mature lymphocytes with few scattered eosinophils and admixed monolobated to multilobated large classical RS and RS like cells. The small mature lymphocytes were predominantly CD20 and CD23 positive along with dim positivity for CD5 and negative Cyclin D1 expression. Ki67 was high in the pseudo proliferation centres only. The RS cells showed diffuse membranous expression with Golgi zone accentuation of CD30, diffuse MUM-1 and diffuse nuclear expression of PAX-5. While a few RS cells also revealed CD15 positivity, they were negative for CD45 and EBV immunohistochemistry (IHC). T cell rosettes around RS cells were identified on PD1 IHC, along with CD3 and CD5 which also highlighted background mature T-lymphocytes. Together with the bone marrow FCM findings, a final diagnosis of Richter's transformation (in form of classical Hodgkin lymphoma) in a case of CLL was considered. In view of the patient's age, no co-existent comorbidities, six cycles of ABVD chemotherapy (Injection Adriamycin 25 mg/m²; Injection Bleomycin 10 IU/m²; Injection Vinblastine 6 mg/m² and Injection Dacarbazine 375 mg/m²) were planned and started. Currently the patient is doing well after completion of first cycle of chemotherapy and remains on follow-up until completion of 4th cycle of chemotherapy, after which response assessment will be done and the remaining two cycles will be administered.

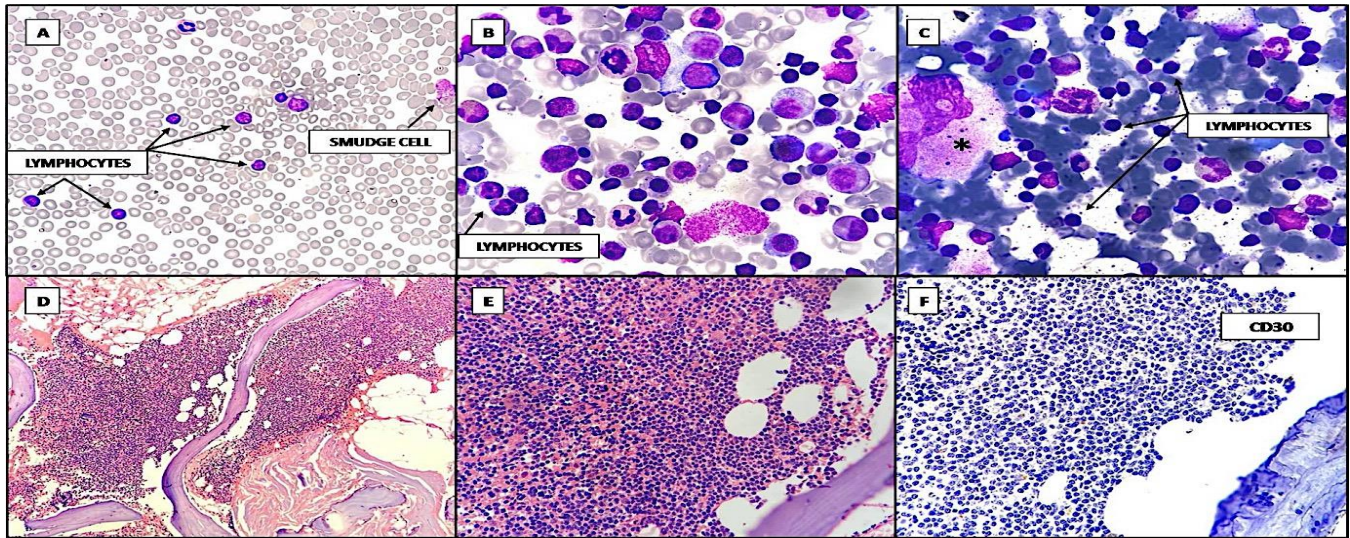


Figure 1: **[A]** Peripheral Smear (20x) showing absolute lymphocytosis with small mature monomorphic lymphocytes and few smudge cells; **[B]** Bone marrow aspirate (100x) and **[C]** Bone marrow imprint smears (100x) showing marked lymphocytosis with intermixed normal trilineage hematopoiesis; * showing a megakaryocyte; **[D]** Bone marrow biopsy (10x) showing sheets of small lymphoid cells with interspersed normal hematopoietic elements, as visualized in **[E]** on higher magnification (40x); **[F]** Immunohistochemistry for CD30 (Clone: Ber-H2; Dako) was negative. No Reed Sternberg (RS)/ RS like cells identified.

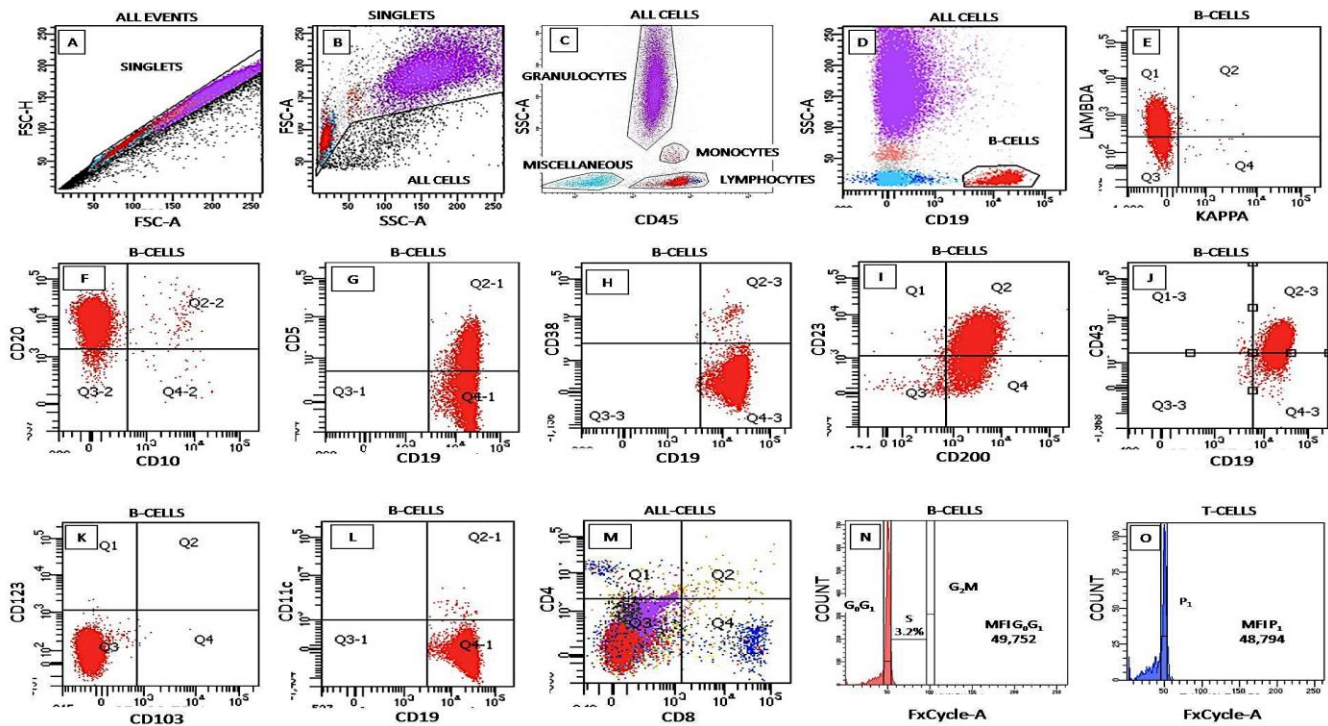


Figure 2. Bone marrow (BM) flowcytometry (FCM) showing **[A]** sequential gating strategy to select “singlets” using forward scatter (FSC)-area (A) and height (H); **[B]** selecting all viable cells using side scatter-A and FSC-A; **[C]** CD45-SSC showing granulated granulocytes in magenta, monocytes in orange, abnormal B-lymphocytes in red, remaining T-lymphocytes in blue and CD45 negative erythroid cells in cyan; **[D]** abnormal B-cells gated using CD19-SSC **[E]**; positive for CD20, negative for CD10 **[F]**; positive for CD5 **[G]**; negative for CD38 **[H]**; positive for CD23 and CD200 **[I]**; positive for CD43 **[J]**; negative for CD123, CD103 **[K]** and CD11c **[L]**; **[M]** Rest of the T-cells showing CD4:CD8 ratio of 1:2; **[N & O]** DNA Analysis using FxCycle™ Violet dye showing diploid B-cells, DNA index: Median fluorescence intensity (MFI) G₀G₁ of abnormal lambda restricted B-Cells to MFI G₀G₁ normal T-cells= 1.02 with a high S-Phase fraction of 3.2%.

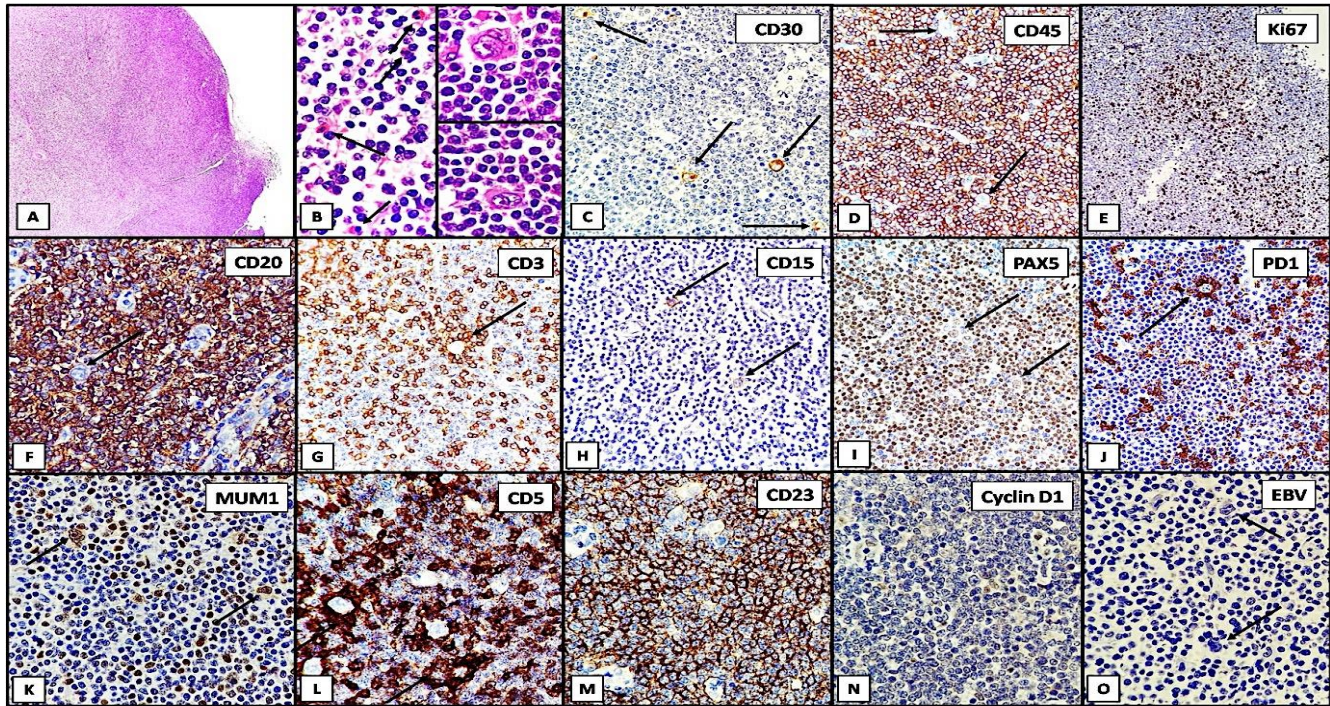


Figure 3. **[A]** Scanner view (4x, H&E) showing complete effacement of the lymph node architecture by **[B]** an infiltrate composed of small mature lymphocytes with few scattered eosinophils (arrows) and admixed monolobated to multilobated large classical Reed-Sternberg (RS) and RS like cells with eosinophilic macronuclei. (100x, H&E) No necrosis seen. No granulomas seen; **[C]** CD30 (clone Ber-H2, Dako) showing RS cells (arrows) with diffuse membranous expression and Golgi zone accentuation; **[D]** CD45 (clone RP2/18, Ventana) RS cells (arrows) negative, diffusely positive on background small lymphoid cells; **[E]** Ki67 (clone 30-9, Ventana) high in pseudo-proliferation centres; **[F]** CD20 (clone L26, Ventana) RS cells (arrow) negative, diffusely positive on small B-lymphocytes; **[G]** CD3 (Polyclonal, Dako) RS cells (arrow) negative with a T cell rosette around RS cells, positive on background T-lymphocytes; **[H]** CD15 (clone Carb-3, Dako) Positive on RS cells (arrow); **[I]** PAX-5 (clone DAK Pax-5, Dako) Diffusely positive on RS cells (arrow) and on small B-lymphocytes; **[J]** PD1 (clone SP263, Ventana) showing T cell rosette around RS cells (arrow); **[K]** MUM-1 (clone BC5, Biocare) Diffusely positive on RS cells (arrows); **[L]** CD5 (clone 4C7, Dako) showing T cell rosettes around RS cells (arrows), dim positivity on B-cells (dotted arrow) with strong positivity on background T cells; **[M]** CD23 (clone DAK -CD23, Dako) Diffusely positive on B-cells; **[N]** CyclinD1 (clone EP12, Dako) Negative; **[O]** EBV (clone CS.1-4, Dako) Negative on RS cells.

DISCUSSION

RT was first described in 1928 by Maurice Richter as the development of an aggressive large-cell lymphoma in the setting of underlying CLL/SLL. For the diagnosis of RT, histopathological examination is the gold standard. Although DLBCL is the most common histology seen in patients with RT (2-8% cases), T cell lymphomas, multiple myeloma, Burkitt's lymphoma and lymphoblastic lymphoma have also been reported. Hodgkin variant RT has been reported in <1% RT cases with only about 100 cases documented in literature till date¹⁻⁴. It has been reported in older (age range 49-81 years) male patients (male: female ratio of 3.5:1). Histologically, two types of Hodgkin's RT have been described, type-I in which scattered or clustered RS cells are seen in a background of CLL cells and type-II

category, where the RS cells are found within a polymorphous reactive background, thereby making it indistinguishable from de novo HL, the most common histological subtypes being mixed cellularity, followed by nodular sclerosis, lymphocyte depleted, and lymphocyte predominant/ rich³. The median time interval between CLL diagnosis and HL-RT is 4.3 years (0 to 17.7 years) with or without prior CLL therapy in 90% of these cases, while <10% cases demonstrate simultaneous co-occurrence at initial diagnosis⁵⁻⁸.

The very existence of type-I pattern has been debated, especially considering the existence of "B-CLL with RS like cells". However, these cases of B-CLL with EBV-driven RS like cells, similar to Type-I RT, do not show the HL reactive milieu, however the typical T-cell rosettes around RS- cells are lacking in the

former and are rather surrounded by neoplastic B cells^{5,9}. The type-I pattern may be considered a relatively early event in the evolution of the CLL to HL based on the following facts: 1) The diagnosis of a type I Hodgkin-like lesion is the initial finding leading to a diagnosis of CLL; only 27% of patients have a prior diagnosis of CLL as opposed to 73% with a type-II pattern; 2) The median age of type-I patients (62 years) is 11 years younger than type II (73 years); 3) The overall survival (approximately 44 months) is similar for both type I and type II from the time of the HL diagnosis and is not influenced by prior treatment; 4) Type-I pattern appears to progress to type-II lesions over time⁸⁻¹⁰. Our patient, who was a 60-year-old male, presented with concomitant HL-RT in a previously undiagnosed and untreated CLL. He likely falls in the type-I HL RT category and is not CLL with RS like cells, as primarily the background of lymph node was composed of CLL cells, lacking the typical reactive milieu of HL, however scattered eosinophils were seen, along with interspersed monolobated and multilobated classical RS cells with eosinophilic macro-nucleoli, having typical immunoprofile of classical HL and T cell rosettes around them. Though EBV positivity is seen in both Type-I RT and CLL with RS like cells, our case was EBV IHC (LMP1) negative, which could have been picked up with more sensitive *in situ* hybridization (ISH) for EBV-encoded RNA (EBER)-1 and polymerase chain reaction (PCR) for EBV¹¹ which were not performed. Interestingly, the diagnosis of CLL/SLL can be confused with lymphocyte rich CHL (which was made outside), in particular, the rarer diffuse variant^{1,10}. Numerous risk factors predictive of CLL/SLL progression to HL-RT have been entailed in literature including sudden clinical deterioration; increase in lymphadenopathy at one or more sites (often abdominal); splenomegaly; extranodal involvement; worsening "B" symptoms (i.e. fever, night sweats, weight loss); monoclonal gammopathy; elevation of serum lactate dehydrogenase (LDH); increased beta-2-microglobulin, anaemia; thrombocytopenia; over-expression of CD38 by FCM ($\geq 30\%$); genetic factors including loss of 11q (ATM) and 17p (p53), as well as chromosome 20, acquisition of trisomy 12, and losses of 8p and chromosome 9; $SUV_{max} > 5$ in PET/CT predictive of RT and $SUV_{max} > 10$ suggestive of poor

prognosis; prior chemotherapy for CLL, particularly purine analogue based¹²⁻¹⁶.

Our patient was a de novo CLL with concurrent HL-RT, who presented with low-grade fever and history of weight loss, hepato-splenomegaly with multiple supra-infradiaphragmatic lymph nodes (SUV_{max} up to 4.6). There was no anaemia or thrombocytopenia and CD38 was not over-expressed by FCM. Baseline LDH, beta-2-microglobulin levels, cytogenetic and molecular studies were not available.

Though we did not perform micro-dissection experiments, certain studies incorporated micro-capture dissection and PCR studies to elucidate whether the RS cells and CLL/SLL cells were clonally related or not. Only ZAP-70 expression of the CLL/SLL cells, but not EBV status or morphological pattern was correlated with clonal relatedness. CLL is derived from either immunoglobulin V_H gene unmutated or mutated (antigen-experienced) post-germinal centre B-cells. HL is thought to originate from germinal centre or post-germinal centre B-cells with evidence of somatic V_H hypermutation. RS cells from all ZAP-70 positive (IGV_H unmutated) CLL cases were clonally unrelated, whereas RS cells from ZAP-70 negative (IGV_H mutated) CLL cases share the same clonal origin as that of associated CLL. Infrequently, clonally unrelated RS cells can occur in ZAP-70 negative (IGV_H mutated) CLL as a true secondary neoplasm^{10,17}.

Despite the available different chemotherapeutic regimens, treatment is challenging and the prognosis of HL-RT in CLL remains poor, compared with de novo HL. The majority of patients reported in the literature have received combination chemotherapy targeted at HL, including ABVD, MOPP (Methotrexate, Oncovin, procarbazine and prednisone), CVPP (Cyclophosphamide, vinblastine, procarbazine and prednisone \pm involved field radiation), CHOP \pm R (Cyclophosphamide, doxorubicin, vincristine and prednisone \pm rituximab) or FCR (Fludarabine, cyclophosphamide and rituximab) with a $< 50\%$ response rate in the largest series and some long-term survivors. Those who achieve a complete remission (CR) are observed until progression while those who do not achieve a CR are offered serial regimens used for refractory HL and further, non-myeloablative allogeneic hematopoietic stem cell transplant in first CR due to short remission duration. A number of novel agents are also being tried including anti-EBV agents,

monoclonal antibodies directed against CD30 (brentuximab vedotin) but with limited success. Disease response and clinical outcomes are worse than in *de novo* HL (particularly in patients previously treated for CLL) but better than in DLBCL RT^(2,7,18,19). Currently, our patient is doing well after completion of first cycle of chemotherapy and would remain on follow-up until completion of 4th cycle of chemotherapy, after which response assessment will be done and the remaining two cycles will be administered.

CONCLUSION

HL-RT occurring in CLL is a rare event with heterogeneous clinical presentation, morphology, clonal origin, disease course, prognostic features and survival.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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