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Case Report

Richter transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma to composite diffuse large b-cell lymphoma and hodgkin lymphoma: a case report and review of literature

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1. Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a B-cell lymphoproliferative disorder characterized by monoclonal small mature lymphocytes with round nuclei, clumped chromatin, inconspicuous nucleoli and scant cytoplasm. It has characteristic morphologic and immunophenotypic features including small lymphocyte size with round nuclei and clumped chromatin pattern that co-express dim CD20, CD5 and CD23 [1]. While initially believed to be an indolent disease, it is now known that CLL/SLL is biologically heterogenous with highly variable clinical behavior. Rai and Binet staging systems are used clinically to stratify CLL/SLL into prognostic subgroups. In addition, a set of immunophenotypic and molecular prognostic markers, such as expression ZAP70, CD38 and CD49d, IgVH mutation and cytogenetic aberrations, are also used to predict outcome as reviewed by Rai et al. [2].

Richter's transformation occurs in 2–10% of CLL/SLL [3,4] and is associated with a dismal prognosis with median survival of 5–8 months [3] that necessitates aggressive immunochemotherapy with allogeneic hematopoietic cell transplantation [4]. It is clinically suspected when CLL/SLL patients present with rapidly enlarging lymphadenopathy, increasing B symptoms and laboratory abnormalities, especially with elevated lactate dehydrogenase (LDH) [4,5]. The diagnosis is confirmed by pathologic evidence of diffuse large B-cell lymphoma (DLBCL) or less frequently Hodgkin's lymphoma (HL) [6,7]. Composite transformation of CLL/SLL into synchronous non-Hodgkin lymphoma and Hodgkin lymphoma is an exceeding rare phenomenon with only 4 reported cases in the literature (Table 1). All four patients are elderly male with median age of 75 years and presented with rapidly progressing lymphadenopathy. Two of the four patients received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy and one received rituximab in addition to CHOP. Of the three patients who received chemotherapy, one showed complete response at the last follow-up; two died at 11 months and 30 months after the diagnosis of Richter transformation. Here, we report another case of EBV-positive DLBCL and Hodgkin lymphoma arising synchronously in older patient with CLL/SLL.

2. Case report

An 82-year-old female with a remote history of breast cancer treated with mastectomy, radiation and chemotherapy first presented in 2016 with an asymptomatic lymphocytosis. Flow cytometry performed on peripheral blood demonstrated a monoclonal B cell population that is positive for CD20 (dim), CD5, CD23 and surface lambda and was diagnosed as CLL/SLL. Additional cytogenetic/FISH analysis revealed deletion of 13q and 17p. IgVH was mutated. CT scan showed small-volume periportal, retroperitoneal and pelvic lymphadenopathy, consistent with Rai stage 0. No therapy was initiated at that time. One year after the initial diagnosis, in 2017, she presented with rapidly increased lymphocytosis and found to have FGD-avid diffuse lymphadenopathy including axillary, mediastinal, hilar, intra-abdominal and pelvic areas as demonstrated on PET/CT scan. She remained asymptomatic and had excellent performance status. She underwent a left axillary lymph node excisional biopsy for pathologic evaluation.

The biopsy showed an enlarged lymph node (5.5 cm) with nodal architecture completely effaced by a predominant population of small atypical cells with round nuclei, clumped chromatin, inconspicuous nucleoli, scant cytoplasm and low mitotic activity (Fig. 1, A). A series of well controlled immunohistochemical stains demonstrated that these cells are positive for dim CD20, PAX5, CD5, CD23 and BCL2; and negative for CD3, BCL6, CD10, MYC, MUM-1, CD30 and CD15. Proliferation index, as measured by Ki-67, is approximately 20% (Fig. 2, upper left of the juxtaposing figure). These morphologic and immunophenotypic findings are of small lymphocytic lymphoma. Scattered throughout and closely admixed with small lymphocytes a population of large atypical cells with folded nuclei, open chromatin, prominent eosinophilic nucleoli and abundant pale cytoplasm, morphologically resembling Reed-Sternberg cells (Fig. 1 D). Many binucleate Reed-Sternberg forms are also seen. No fibrosis or increased

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Table 1
Summary of the literature reporting composite richter transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Gender	Age (years)	Stage at CLL diagnosis	Clinical presentation	Time to RT	Type of RT	EBV infection	Treatment	Outcome	References
Male	75	Rai stage II	Constitutional symptoms Generalized LAD	6 years	DLBCL HL	Positive	R-CHOP	Respond to treatment	10
Male	76	Not known	Generalized LAD	4 years	ALCL HL	Negative	Not known	Not known	11
Male	51	Not known	Constitutional symptoms Inguinal LAD Bone mass	3 years	DLBCL HL	Not known	CHOP	Died after 11 months	12
Male	75	Rai stage IV	Splenomegaly Axillary LAD	15 months	PLL HL	Positive	CHOP	Died after 30 months	9

LAD, Lymphadenopathy; RT, Richter transformation; PLL, prolymphocytic lymphoma; CHOP, Cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; HL, Hodgkin lymphoma; DLBCL, Diffuse large B-cell lymphoma.

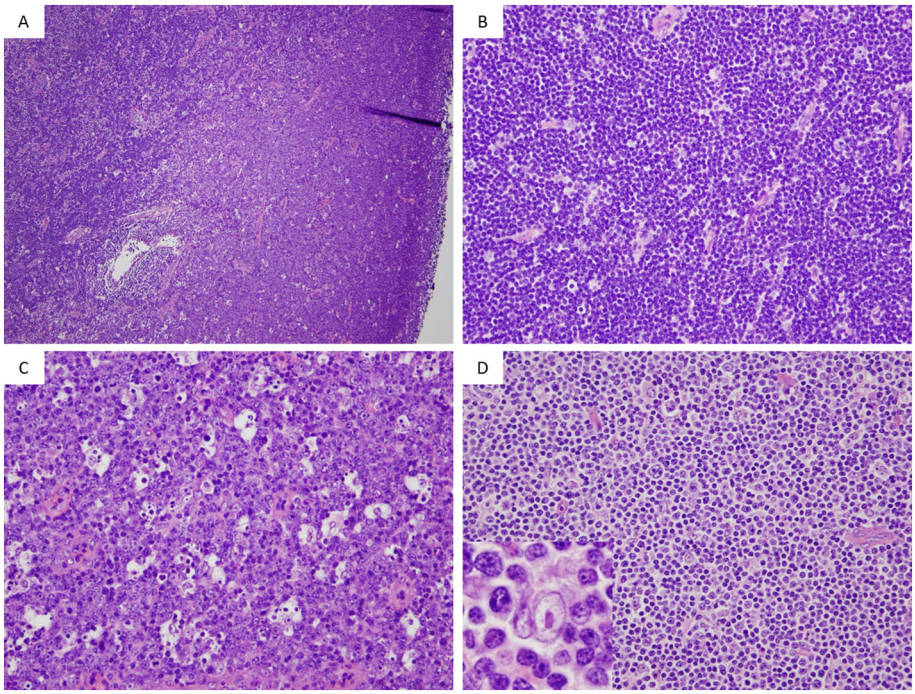

Fig. 1. Histologic components of the patient's composite lymphoma. At scanning magnification (A, 4×), a low-grade (upper left) and a high-grade component (upper left) can be seen closely juxtaposed to each other. At high magnification, the low component is composed of diffuse small lymphocytes characteristic of CLL/SLL (B, 40×). In contrast, the high-grade component is comprised of pleomorphic large cells with increased mitotic activity, numerous karyorrhexis and tingible-body macrophages (C, 40×). In other areas, classic Reed-Sternberg cells (D, inset) are found scattered in a background of CLL/SLL (D, 40×; *inset* 100×). *Hematoxylin and eosin (H &E) stain.*

eosinophils is identified. These cells are positive for PAX5 (dim), EBER, CD30, and CD15 (subset), consistent a Hodgkin lymphoma (Fig. 3).

Sharply demarcated from these areas (Fig. 1, A), a few diffuse areas were identified that are composed of intermediate-to-large cells with irregular nuclei, open chromatin, small nucleoli, scant cytoplasm and high mitotic index. Karyorrhexis is prominent in these areas with numerous tingible body macrophages creating a classic 'starry sky' pattern (Fig. 1, C). In contrast to other areas, these large cells are distinctively reactive for bright CD20, bright PAX5, BCL6, MYC, MUM1, and CD10; and are negative for CD3, BCL2, CD30, and CD15. Ki-67 proliferation index marker highlighted > 90% of cells. In situ hybridization for EBV–encoded RNA transcript (EBER) is positive in most large cells (Fig. 2, lower right). FISH study for MYC gene rearrangement is negative. The diagnosis of morphologic transformation of CLL/SLL was made and. The patient received 6 cycles of R-CHOP as standard therapy for Richter transformation.

3. Discussion

Composite lymphoma refers to synchronous involvement by two or more distinct lymphomas and is an uncommon entity [8]. Morphological transformation of CLL/SLL to a composite lymphoma is exceedingly rare with only a few reported cases in the literature [9–12] (Table 1). In 2 of the 4 case reports, synchronous involvement by DLBCL and HL was described. Clonal relatedness of these lymphomas to CLL/SLL was not investigated [10,12]. In the third case, the authors described composite HL and anaplastic large cell lymphoma (ALCL) arising from a CLL/SLL. Although morphologically and immunophenotypically distinct, all three components demonstrated identical IgH gene rearrangement, suggesting a common precursor [11]. In addition, a composite prolymphocytoid lymphoma and HL was found to be the transformed component [9]. Here, we describe a patient with long standing history of CLL presenting with a newly diagnosed adenopathy which revealed composite DLBCL and HL with both components demonstrating classic morphology and immunophenotype for their types. Interestingly, in situ hybridization for EBER was positive in both DLBCL and HL components, suggesting an EBV-mediated mechanism, which was described in 16–23% of Richter's transformation [13,14] and found in two of the three composite-RT cases [9–11]. EBV-positive HL is usually clonally distinct from the underlying CLL/SLL and arises as an independent, secondary malignancy [7]. In our case, the HL component does not have the characteristic inflammatory background and exhibits features of the so-called Type 1 "Hodgkin-like lesion," which is thought to represent an early stage of transformation with similar prognosis to the bone fide "Type 2 Classical HL-RT" [6].

Transformation to EBV-positive DLBCL is seen in 16–23% of RT, and primarily associated with IgHV-hypermutated CLL [13,14]. It is more frequently to be clonally-unrelated to the underlying CLL/SLL