Concurrent Presentation of Hairy Cell Leukemia and Mantle Cell Lymphoma (Leukemic Non-Nodal Variant): An Extremely Rare Composite Lymphoma

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Abstract

Herein, we describe the clinicopathologic and genetic characteristics of the first report of simultaneous bone marrow involvement by classical hairy cell leukemia (HCL) and leukemic non-nodal variant of mantle cell lymphoma (L-NN-MCL) with t(11;14)(q13;q32) with BRAF mutation and deletion of TP53. A 40-year-old asymptomatic man was investigated for incidental neutropenia and thrombocytopenia. Flow cytometry showed two distinct monotypic B-cell populations: one expressed CD19 (bright), CD20 (bright), FMC7, CD103, CD25, CD11c, CD123, and IgD (bright) and showed kappa light chain restriction (bright), consistent with HCL and the other kappa-restricted CDS/CD10-negative B-cell population with distinctive immunophenotypic features. The bone marrow biopsy is infiltrated by an abnormal B-lymphoid infiltrate with different patterns of infiltration in different marrow areas. Fluorescence in situ hybridization (FISH) analysis revealed a CCND1/IGH rearrangement, t(11;14)(q13;q32), and deletion of TP53. The BRAF V600E missense mutation was detected by quantitative real-time polymerase chain reaction (PCR). The diagnosis of a composite B-cell neoplasm was composed of HCL together with a second CDS/CD10-negative monotypic B-cell population, with CCND1/IGH fusion, favoring the 2016 WHO new category of L-NN-MCL (CD5/SOX11-negative). Treatment with cladribine and rituximab normalized the blood counts within 6 weeks without significant side effects. L-NN-MCL is one of the smoldering MCL subtypes, recently listed in WHO 2016 as a separate variant, with a particular set of unique features and a less aggressive clinical course compared to classical MCL. To date, the clinicopathological features (including the bone marrow findings) of L-NN-MCL have not been sufficiently characterized in the literature. We describe the first report of synchronous presentation of HCL and L-NN-MCL. This case represents a real challenge from the biologic, diagnostic and therapeutic point of views, due to extremely rare combination of two distinct uncommon B-cell neoplasms. The study of composite lymphomas offers the opportunity to evaluate the etiology and the clonal interrelationship involved in the pathogenesis/evolution of lymphomas.

Keywords: Hairy cell leukemia; Leukemic non-nodal mantle cell lymphoma; Composite lymphoma

Introduction

Composite lymphoma (CL), defined as two or more distinctly different lymphomas occurring concurrently at the same organ or tissue at the time of presentation, is a rare event with estimated incidence at 1-4% of lymphoma presentations [1]. Hairy cell leukemia (HCL) is an uncommon but distinct B-cell lymphoid neoplasm [2]. Morphologically, hairy cells (HCs) are characterized small- to medium-sized with oval or indented nuclei, an abundant cytoplasm and typical hairy-like projections. HCL has a unique immunophenotypic (IPT) characterized by clonal expansion of B cells with bright CD19, CD20, CD22, and CD200 expression. HCs are usually negative for CD5, CD23, and CD10 and characteristically positive for CD11c, CD103, CD123, and CD25.

Underpinning the characteristic morphologic and phenotypic features of classical HCL are activating mutations in the kinase domain of the BRAF gene. The somatic V600E BRAF mutation in exon 15 is present in almost 100% of classical HCLs [3] and is now considered the molecular hallmark of HCL and an early genetic event that can be used as a novel diagnostic tool and an opportunity for therapies targeting of BRAF (BRAF inhibitors) [4]. The late-activated post-germinal center memory B cell is considered as the cell of origin for HCL [5].

On the other hand, mantle cell lymphoma (MCL) is another B-cell malignancy that makes up approximately 6% of all the non-Hodgkin lymphomas [6]. MCL is derived from naive, pre-germinal center cells of primary follicles or the mantle zone of secondary follicles. It presents most commonly with generalized lymphadenopathy, hepatosplenomegaly, and extra...
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J Hematol. 2022;11(1):21-28

nodal disease which primarily involves the bone marrow (BM) and gastrointestinal tract [2]. MCL typically possesses the characteristic t(11;14)(q13;q32) chromosomal translocation leading to overexpression of cyclin-D1 as the chief genetic event, and provides an exceptional marker for diagnosis. MCL cells conventionally express CD5 and cyclin-D1 while lacking CD10, CD23, and BCL-6 expression.

Traditionally, MCL has been considered to have a more aggressive clinical course with shorter survival (median survival of 3 - 5 years) [2, 7], compared with other indolent lymphomas (including HCL).

Recent data show that MCL is in fact a heterogenous entity with up to 30% of MCL patients having a more indolent clinical course and proliferation activity [8], with survival exceeding 7 - 10 years referred to as smoldering MCL [9]. Various clinicopathologic variables aid in the stratification of patients with MCL; these include baseline clinical features Mantle Cell International Prognostic Index (MIPI), leukemic non-nodal and in situ presentation, pathological features including blastoid morphology, Ki-67 proliferation index, SOX11 expression, and genetic aspects (immunoglobulin mutation status, TP53, and CDKN2A deletion) [10]. Leukemic non-nodal MCL (L-NN-MCL) is one of the smoldering MCL subtypes, recently listed in WHO 2016 as a separate variant, with a particular set of unique features and a less aggressive clinical course compared to classical MCL [2, 11]. To date, the clinicopathological features (including the BM findings) of L-NN-MCL have not been sufficiently characterized in the literature.

We describe the first report of synchronous presentation of HCL and L-NN-MCL. This case represents a real challenge from the biologic, diagnostic and therapeutic point of views, due to extremely rare combination of two distinct uncommon B-cell neoplasms.

Case Report

Investigations

A 40-year-old man, previously healthy and asymptomatic, was referred to hematology clinic after the incidental finding of thrombocytopenia and neutropenia in his routine laboratory workup. The patient denied any fever, weight loss, night sweats or bleeding tendency. He had a previous history of lymphadenopathy 4 years previously, when a lymph node (LN) biopsy revealed reactive follicular hyperplasia.

Abdominal ultrasound revealed mild splenomegaly (13 cm). A fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan showed an enlarged spleen (15 cm) with intense FDG uptake with standardized uptake value (SUV) max of 5.6 compared to liver (2.1). A small (1.5 cm) axillary LN with barely appreciated tracer uptake (SUV max of 2.2) was detected, probably reactive.

Diagnosis

Peripheral blood (PB) smear (Fig. 1a) showed moderate neutropenia and thrombocytopenia with about 7% abnormal lymphoid cells (HCs) of small/medium to large size with oval/indented/ kidney shaped nuclei, dispersed nuclear chromatin, few small nucleoli with abundant pale cytoplasm and hairy-like projections in some forms.

BM aspirate (Fig. 1b) was infiltrated by about 16% abnormal lymphoid cells (HCs). In addition, there were some mature looking lymphocytes (about 18%) including plasmacytoid forms and a few forms with irregular plasmacytoid projections.

Flow cytometry (FCM) (on BM aspirate) (Fig. 2) showed a population of monotypic B cells comprising about 6% showing high light side scatter and expressing CD19 (bright), CD20 (bright), CD79b, FMC7, CD103, CD25, CD11c, CD123, IgM, and IgD (bright) and showing kappa light chain restriction (bright). This monotypic population was negative for CD5 and CD10 with no significant expression of CD38, CD23 or CD43. This IPT is consistent with HCL.

In addition, the analysis revealed a second population of kappa-restricted monotypic B cells (about 10%), showing lower light scatter and expressing CD19, CD20, FMC7, CD79b, IgM, IgD and CD38 with partial expression of CD43 (heterogenous). This population was negative for CD5, CD23, CD10, CD25, CD11c, CD103 and CD123.

BM biopsy (BMB) (Fig. 3) showed variable cellularity ranging between marked hypocellularity (< 5-20%) cellularity in few spaces alternating with normocellular and mildly hypercellular areas (70-85%).

The BM was infiltrated with many B-lymphoid cells, but with different patterns of infiltration in different marrow areas. Some areas show widely spaced infiltrate composed of small- to medium-sized lymphoid cells with kidney shaped/indented nuclei and abundant cytoplasm giving the fried-egg appearance. Other BM spaces showed an interstitial infiltration with small-sized lymphoid cells. The abnormal lymphoid cells are positive for CD20, PAX-5, and showed partial positivity for DBA-44, cyclin-D1, CD25 and annexin A1. Positivity for CD20 and PAX5 exceeded that for DBA44, cyclin-D1 and CD25. No increase in plasma cells was highlighted with CD138 immunostain.

The fluorescence in situ hybridization (FISH) analysis (Fig. 4a, b) on BM revealed an abnormal hybridization signal pattern consistent with CCND1/IGH rearrangement, t(11;14) (q13;q32) and deletion of TP53 in 7% of the cells analyzed.

Because of its challenging nature, the whole diagnostic material was referred abroad to Mayo Clinic reference laboratories for second opinion, where they performed immunohistochemistry for BRAF and repeated cyclin-D1 immunostain, and confirmed the diagnosis of a composite B-cell neoplasm composed of HCL together with a second monotypic B-cell population, CD5/CD10-negative with CCND1/IGH fusion by FISH, favoring the 2016 WHO new category of L-NN-MCL.

A low level positive BRAF V600E missense mutation was detected by quantitative real-time polymerase chain reaction (PCR) confirming the presence of a minor HCL clone.
Immunoglobulin heavy chain variable region gene rearrangement analysis showed two distinct clonal B-cell populations, a dominant 335 bp IGVH (FR1) clone and a 317 bp IGVH (FR1) subclone (Fig. 4c).

Taken together, the genetic results support the presence of two clonal B-cell populations, a dominant clone with a TP53 deletion and CCND1/IGH rearrangement and a second BRAF V600E mutated B-cell subclone.

**Treatment**

The multidisciplinary leukemia team supported the approach of giving cladribine first to treat the HCL component and then to reassess the mantle cell component afterwards.

Initial treatment was aimed at the HC component and consisted of cladribine 0.14 mg/kg intravenous (IV) daily for 5 days and rituximab 375 mg/m² IV weekly for eight doses.

**Follow-up and outcomes**

The thrombocytopenia and neutropenia resolved within 6 weeks of starting treatment without significant side effects and the patient achieved end of treatment complete remission confirmed by PET/CT and BMB.

**Discussion**

HCL is an uncommon, chronic B-cell leukemia, first reported as a distinct entity in the 1950s [1, 2]. HCL accounts for 2% of lymphoid leukemias, with a male predominance and median age at diagnosis of 58 years. Classical HCL and its variant form (HCL-V) are now regarded as separate entities [3], with different cytological, hematological and immunophenotypic features. BRAF V600E mutation, present in virtually 100% of cases of classical HCL [4], is regarded as a disease-defining event.

This case represents a rare model of CL combining two distinct B-cell neoplasms (HCL and MCL) and the first reported description of HCL and L-NN-MCL. The divergent morphology, different histopathologic infiltration pattern and different immunophenotypic features (by FCM and immunohistochemistry (IHC)), confirmed by molecular genetics findings, all supported the presence of two distinctive types of
Although both clones were kappa-restricted, the FCM immunophenotyping had clearly separated them based on different cell characteristics (size and complexity) and distinct IPT (HCL and non-HCL clones). The detection of \textit{CCND1-IGH} fusion by FISH and a second immunophenotypically distinct, clonal B-cell population by FCM and given that \textit{CCND1-IGH} fusion is rarely in HCL, the upregulation of cyclin-D1 expression detected by IHC stems from a different pathophysiological process, and this would support the presence of a second sepa-
rate clonal process. With this information, based on FCM IPT, the population, harboring the CCND1-IGH fusion is probably the (non-HCL) CD5/CD10-negative population by FCM. The presence of the translocation would then support a diagnosis of MCL, probably L-NN-MCL.

The differential diagnosis of CD5/CD10-negative lymphomas would classically include marginal zone lymphoma and lymphoplasmacytic lymphoma, among other mature B-cell neoplasms that may present with an atypical IPT. However, no pathologic, genetic or clinical evidence for any of the mentioned categories was found.

In both neoplasms, the main tumor burden was localized in BM (and likely the spleen), whereas the LNs were minimally (if at all) involved.

Clinically L-NN-MCL involves the PB, BM and sometimes the spleen. However, this variant is characterized by reduced cell adhesion/infiltrative properties and hence lacks significant lymphadenopathy (defined as peripheral LNs < 1 - 2 cm and absent lymphadenopathy on CT) [12-14]. A thorough radiological staging CT or, when available, PET/CT scan to demonstrate the absence of significant lymphadenopathy is required for the diagnosis of L-NN-MCL variant.

Morphologically, the L-NN-MCL leukemic cells are small, resembling chronic lymphocytic leukemia (CLL) type cells with no specific morphologic features. L-NN-MCL tends to present with a lower MIPI/Ki-67 proliferation rate and harbors somatic Ig hypermutation [14], demonstrating their generally less aggressive features. CD5 negativity is more frequent than in classic MCL [1]. In addition, recent published data also show decreased SOX11 expression in patients with indolent (smoldering) MCL including L-NN-MCL [12-15].

Patients with L-NN-MCL tend to have a more favorable...
outcome than those with classic MCL (median survival: 79 months). A “watch and wait” approach or initially less intensive treatment options can be successful for long periods [12-14].

Some cases of L-NN-MCL show progressive disease with or without tissue involvement, and/or transformation to a morphologically aggressive variant. This evolution is frequently associated with acquisition of TP53 mutations (17p13) or other oncogenic mutations [16].

The case reported here although clinically indolent, has a low level of TP53 mutation detected, this being a worrisome finding that may imply a more aggressive clinical course in the future.

CLs involving HCL are rare with scarce case reports, mostly T-cell lymphomas presenting in association with HCL. The reported cases include associated peripheral T-cell lymphoma [17], hepatosplenic T-cell lymphoma [18], and cutaneous T-cell lymphoma [19]. Among B-cell neoplasms, B-CLL has been the most common subtype reported in association with HCL [20-22].

Synchronous development of HCL and MCL is extremely rare with a single case reported in 2019 [22]. The group demonstrated independent origin of two tumor components and proved the different way of their differentiation. Only a single case of CL involving L-NN-MCL in association with gamma-delta T-large granular lymphocytic leukemia in a patient with rheumatoid arthritis has been reported [23]. No previous reports of HCL with L-NN-MCL have been found.

Among the theories explaining the pathogenesis of CL, we propose that the immune dysregulation and immunodeficiency status commonly associated with HCL seem the most likely to explain the propensity to develop a secondary neoplastic clone (MCL) in our case.

It appears less likely that there has been transformation from one lymphoma type to another in this context as both components (HCL and L-NN-MCL) are considered to be low-grade lymphomas. These two lymphoid malignancies also have different genetic drivers, decreasing the likelihood of the possibility of a common genetic predisposition for both components. Additionally, the presence of completely different genetic drivers (in each lymphoma component) would exclude the possibil-

![Figure 4. Interphase FISH demonstrating IGH/CCND1 rearrangement (a): IGH (14q32) labelled with spectrum green, CCND1 (11q13) labelled with spectrum orange show dual fusions signals as result of IGH/CCND1 fusion (yellow arrow). Loss of a single copy of CEP17/TP53 indicates deletion of TP53 gene on chromosome 17. CEP17 (17p11.1-q11.1) labelled with spectrum green, and TP53 (17p13.1) labelled with spectrum orange (b) (green arrow). PCR-based clonality testing (Invivoscribe Identiclone) was used to identify clonal B-cell populations with primers that target conserved framework (FR) and joining (J) regions of the IGVH genes. Two clonal B-cell populations were identified: a dominant 335 bp IGH VH (FR1) JH clone (red arrow) and a 317 bp IGH VH (FR1) JH subclone (blue arrow) (c). FISH: fluorescence in situ hybridization; PCR: polymerase chain reaction.](image-url)
ity of genetic predisposition for both components.

**Conclusion**

In summary, we describe the first case report of synchronous presentation of HCL and L-NN-MCL. This case represents a real challenge due to extremely rare combination of two separate uncommon B-lymphoproliferative disorders. These two neoplastic processes have different cells of origin, clinical behavior with distinctive morphologic, immunophenotypic, cytogenetic and molecular genetic characteristics; in particular each of these neoplasms has its own unique genetic signature with (t(11;14) in MCL and the **BRAF** mutation in HCL. Two distinct clonal B-cell populations were confirmed by PCR analysis of the **IGVH** gene rearrangements. Further analysis of **IGVH** gene family usage, although not performed here, could help distinguish if these are two independent clones or if both clones share a common germinal cell origin.

**Learning points**

The diagnosis of the HCL component in our case was straightforward, given the characteristic morphology, IPT and genetic features. However, the greater diagnostic challenge was related to the diagnosis of L-NN-MCL component which was overshadowed by a number of atypical features including the lack of CD5 and SOX11 expression in addition to the known frequent expression of cyclin-D1 by HCL cells and absence of lymphadenopathy or other tissue involvement, which added another level of complexity in making the diagnosis. There was a convincing evidence for BM involvement by two distinct lymphomas. The pathologists should be aware about the presence of this variant of MCL (with atypical features) that can be easily missed and necessitates an integrated analysis of multiparametric diagnostic data compiling morphologic, immunophenotypic, cytogenetics and molecular genetics findings.

**Acknowledgments**

We acknowledge the contributions of the Hematology Team in Clinical Hematology Department particularly Dr. Halima El-Omri and Dr. Amna Gamil and we also would like to acknowledge the role of flow cytometry, cytogenetics and molecular genetics teams in the Department of Laboratory Medicine and Pathology, Hamad Medical Corporation.

**Financial Disclosure**

None to declare.

**Conflict of Interest**

None to declare.

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**Informed Consent**

Not applicable.

**Author Contributions**

DSS performed the bone marrow examination, literature review and formulated the paper; FI reviewed the diagnosis and the manuscript; LJF reviewed the clinical data, treatment plans and reviewed the manuscript; FM performed the cytogenetics testing; SA performed the molecular genetics testing and reviewed the manuscript.

**Data Availability**

The authors declare that data supporting the findings of this study are available within the article.

**Abbreviations**

CL: composite lymphoma; HCL: hairy cell leukemia; MCL: mantle cell lymphoma; BM: bone marrow; L-NN-MCL: leukemic non-nodal MCL

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