Composite Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and Mantle Cell Lymphoma; Small Cell Variant: A Real Diagnostic Challenge. Case Presentation and Review of Literature

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Patient: Male, 57-year-old
Final Diagnosis: CLL/SLL and MCL composite lymphoma
Symptoms: Abdominal pain
Medication: —
Clinical Procedure: BM examination
Specialty: Hematology

Objective: Rare co-existence of disease or pathology
Background: Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL) both have a common origin arising from mature CD5+ B-lymphocytes. Their distinction is crucial since MCL is a considerably more aggressive disease. Composite lymphoma consisting of CLL/SLL and MCL has been rarely reported. This type of composite lymphoma may be under-diagnosed as the 2 neoplasms have many features in common, both morphologically and immunophenotypically.

Case Report: We report the case of a 57-year-old male patient who presented with a 4-month history of recurrent abdominal pain and distention with hepatosplenomegaly. Peripheral blood showed a high leukocytes count (46.7×10³/uL) with marked lymphocytosis of 35.0×10³/uL, mostly small mature-looking, with some showing nuclear irregularities, with approximately 3% prolymphocytes. Immunophenotyping by flow cytometry and immunohistochemistry revealed 2 immunophenotypically distinct abnormal CD5+monotypic B-cell populations. Fluorescence in situ hybridization (FISH) on peripheral blood demonstrated IGH/CCND1 rearrangement consistent with t(11;14) in 65% of cells analyzed. Accordingly, based on compilation of findings from morphology, flow cytometry, immunohistochemistry, and FISH, A diagnosis of composite lymphoma consisting of MCL; small cell variant and CLL/SLL was concluded.

Conclusions: We describe a case of composite lymphoma of MCL (small cell variant) and CLL/SLL that emphasizes the crucial role of the multiparametric approach, including vigilant cyto-histopathologic examination, immunophenotyping by flow cytometry and immunohistochemistry, as well as genetic testing, to achieve the correct diagnosis.

MeSH Keywords: Composite Lymphoma • Leukemia, Lymphocytic, Chronic, B-Cell • Lymphoma, Mantle-Cell

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Background

Mantle cell lymphoma (MCL) is a mature B-cell neoplasm comprising about 3% to 10% of non-Hodgkin lymphomas (NHLs) presenting at a median age of about 60 years, most commonly presenting with lymph node involvement and frequently involving bone marrow, liver, spleen, gastrointestinal tract, and peripheral blood (PB). The neoplasm arises from B-cells of the inner mantle zone and is characterized by expression of CD5 and t(11;14)(q13;q32), that brings 2 genes (cyclin D1 and IGH) juxtaposed in more than 95% of the cases with cyclin D1 being overexpressed [1]. Most cases of MCL show no mutations in the IGH variable regions (IGHV), however, some somatic mutation of IGHV has been reported [2]. Morphologically, the common type usually consists of monomorphic lymphoid cells, small to medium in size, showing dispersed nuclear chromatin and often with irregular nuclear contour. Other recognized morphological variants include the blastoid and the plasmorphic (aggressive forms), marginal zone-like, and the small cell variant. The latter is over-represented in patients with leukemic presentation without nodal involvement and could be easily misdiagnosed as CLL [1]. A rare possible new morphological variant mimicking plasma cell-type Castleman disease was recently reported as well [3].

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) accounts for about 7% of all NHLs [4] and in Western countries it is considered the most common leukemia in adults comprising about 25% to 30% of cases [5]. CLL is defined by sustained, persistent monoclonal B-lymphocytosis of more than 5×10⁹/L. In typical CLL, the lymphocytes are characteristically small mature-looking with round nuclei, clumped chromatin, scant cytoplasm with less than 10% prolymphocytes and display distinctive immunophenotype with co-expression of CD5 and CD23. SLL is the term used when lymph node, spleen, or other extramedullary sites are involved with monotypic cells with morphologic and immunophenotypic features of CLL with less than 5×10⁹/L circulating cells. CLL/SLL arise from mature antigen-experienced CD5 positive B-lymphocytes with mutated IGHV genes in 50% to 70% of cases [4].

By definition, composite lymphoma implies the presence of 2 or more morphologic and immunophenotypic different types of lymphoma in a single tissue or organ. Concurrent occurrence of 2 NHL subtypes is more common than synchronous NHL and Hodgkin’s lymphoma (HL) [6]. The incidence of CL is low in general, ranging from 1% to 4.7% [7].

Variable combinations of lymphomas have been reported, however, a composite of MCL and CLL/SLL is rare with as low as 20 cases being reported so far [8–13]. The distinct types of lymphoma can be diagnosed by compilation of morphologic, immunophenotypic, and genetic studies. Immunophenotyping is usually done by immunohistochemistry or flow cytometry, the latter may even be superior in uncovering 2 distinct tumors in the same specimen, in particular, when immunohistochemistry interpretation may not be clearly discriminating.

Case Report

A 57-year-old male patient who was a known case of diabetes mellitus, hypertension, and hypothyroidism, presented with 4 months history of recurrent abdominal pain and distention, not associated with nausea or vomiting or change in bowel habits and any weight loss or night sweating. Physical examination revealed hepatosplenomegaly with no palpable lymphadenopathy. Laboratory investigation revealed a high leukocyte count of 46.7×10⁹/L (normal range 4.00–10.00×10⁹/L), with marked lymphocytosis of 35.0×10⁹/L, normal hemoglobin of 13.5 gm/dL (normal range 13.0–17.0 gm/dL) and mild thrombocytopenia with a platelet count of 115×10⁹/L (normal range 150–400×10⁹/L). Coagulation profile and liver and kidney functions were normal, lactate dehydrogenase (LDH) 237 U/L (normal range 135–225 U/L) and beta 2 microglobulin 2.6 mg/L (normal range 0.97–2.64 mg/L). Abdominal computed tomography (CT) revealed enlarged liver with the right hepatic lobe spanning 18 cm and markedly enlarged spleen measuring 19.8 cm with no focal lesions and multiple subcentimetric retroperitoneal, para-aortic, and mesenteric lymph nodes.

Smear from the peripheral blood (PBS) showed that most of the lymphocytes were small mature-looking, mostly with high nucleocytoplasmic ratio, dense chromatin with no nucleolus or inconspicuous nucleoli. Some cells showed irregular nuclear shape, and few were large with less dense chromatin and single prominent nucleolus (prolymphocytes morphology, comprising approximately 3%) with some smudge cells noted as well (Figure 1A). Flow cytometry on PB revealed 2 abnormal CD5+ monotypic B-cell distinct populations; the first population comprised approximately 58% of the total cells and expressing CD19, CD79b, IgD, IgM, and partial CD23 with lambda light chain restriction. The cells of this population were negative for CD10, CD43, CD200, and CD38. The second smaller population comprised approximately 12% of total cells expressing CD19, CD23, CD5, CD43, CD200, CD38, cBCL2, IgD, IgM, dimmer CD79b, and CD20 (partial dim) with kappa light chain restriction. The cells of this population were negative for CD10 and FMC7. Both monotypic populations were negative for CD11c, CD103, CD25, IgG, and IgA (Figure 1B). These immunophenotype findings indicated involvement by a composite of 2 CD5-positive monotypic B-cell populations; including 12% kappa-restricted monoclonal B-cells with CLL/SLL immunophenotype and 58% CD5-positive lambda-restricted monotypic B-cells with atypical immunophenotype.
Figure 1A. Peripheral blood shows lymphocytosis, mostly small mature-looking, some with irregular nuclear contour and/or inconspicuous nucleolus (inserts). Wright stain 1000×.

Figure 1B. Flow cytometry on peripheral blood revealed an abnormal population of lambda monotypic B-cells (58%, green) expressing CD19, CD20, CD5, FMC7, and CD79b with partial CD23. The cells are negative for CD10, CD43, and CD200. Analysis showed another kappa monotypic population as well (12%, red) expressing CD19, CD20 (partial dim), CD5, CD23, CD43, and CD200 with dim CD79b. The cells are negative for CD10 and FMC7.
Figure 2. (A) Bone marrow biopsy shows hypercellular bone marrow with interstitial lymphoid infiltration. Hematoxylin and eosin (H&E) 40×. (B). The lymphocytes are small to medium, H&E 600×. The cells are positive for PAX5 (+200), CD20 (200×), and cyclin D1 (200×) (mantle lymphoma cells).
Figure 3. Bone marrow biopsy shows large lymphoid aggregates composed mostly of small mature B-cells (CLL cells). Hematoxylin and eosin (H&E) 100×. The cells are positive for PAX5 (100×) and show less positivity for CD20 with many negative or weakly positive cells (100× and 400×). Most of the cells within the aggregates are negative for cyclin D1 (100×), while the cyclin D1 positive cells (mantle lymphoma cells) are at the periphery of the aggregates.
Bone marrow aspirate and biopsy were collected. The aspirate smears were hypercellular and displayed increased lymphocytes (66%) with morphology comparable to that seen in blood. Flow cytometry revealed 59% lambda monotypic B-cells and 10% kappa monotypic cells with immunophenotype profile comparable to peripheral blood. Bone marrow biopsy was hypercellular (~75–95% cellularity) with adequate trilineage hemopoiesis and interstitially increased B-cells; scattered and in clusters, mostly small sized with irregular nuclear contour shown in some forms. One part of the biopsy showed large lymphoid aggregates composed mostly of small mature looking B-cells with few showing irregular nuclear contour. Immunohistochemical stains showed that most of the interstitial B-cells were positive for CD79, CD5, BCL2, cyclin D1, PAX5, and CD20, with comparable degree of positivity for the latter 2 immunostains (Figure 2). On the other hand, within the large lymphoid aggregates, the positivity for PAX5 exceeded that for CD20 and CD79 with many cells showed weak CD20 positivity. Most of the cells within the aggregates were negative for cyclin D1 with cyclin D1-positive cells distributed more at the periphery of the aggregates (Figure 3). The B-cells were negative for BCL6 and CD10.

FISH study on PB using probes for 11q22.4, t(11;14)(q13;q32), 12p11.1-q11.1 and 17p13.1/17p11.1 revealed abnormal hybridization signal pattern consistent with IGH/CCND1 rearrangement, t(11;14), in 65% of cells analyzed. Conventional G-band metaphase analysis revealed 2 cell lines including 41 cells with normal karyotypes and 14 cells with abnormal karyotypes showing a translocation between 11q13 and 14q32, results in IGH/CCND1 fusion; karyotype: 46,XY,t(11;14)(q13;q32) [14]/55,XY,46[41. (Figure 4).

Given the aforementioned cyto-histopathology, immunophenotype and FISH/karyotype findings, a diagnosis of composite lymphoma of 2 CD5-positive mature B-cell neoplasms, including CLL and MCL (small cell variant) were concluded. The MCL represented in the flow cytometry analysis by the large lambda monotypic B-cell population and these were the prevail cells in the marrow. The smaller kappa monotypic B-cell population had an immunophenotype of CLL. The patient was started on Ibrutinib 560 mg daily but unfortunately, he was lost at follow up.

Discussion

Composite lymphoma, which indicate the presence of 2 or more immunophenotypically and morphologically different entities of lymphoid neoplasms in one anatomic site, is an infrequent diagnosis. The combination might include HL with B-cell [14] or a T-cell [6] NHL, B-cell with T-cell NHL [15] or 2 distinct B-cell NHLs [12].
The rare occurrence of composite lymphoma may be attributed at least in part to underdiagnoses, thence reporting. In fact, diagnosis can be a real challenge because one lymphoma component often overshadows the other or may be morphologically indistinguishable as the case with CLL/SLL and the small cell variant of MCL. Hence, a multiparametric approach that covers the clinical presentation, morphologic features, immunophenotypic profile, and genetic findings is vital for accurate diagnosis of lymphoid neoplasms collectively and composite lymphoma in particular. The use of flow cytometry has become an integral and indispensable tool in the pathological diagnosis and classification of mature lymphoid neoplasms. Evidence has emerged in recent years that the use of flow cytometry is a very useful adjunct in the diagnosis of composite lymphoma especially in presence of a smaller monoclonal component [16]. While morphology may identify 2 distinct cellular populations, the key to diagnosis in cases of B-cell NHLs rests mainly on the demonstration of B-cell clonality by light chain restriction, which is extremely difficult by immunohistochemical analysis. Co-expression of cell markers, their level of expression or absence in addition to abnormal patterns have all been useful in suggesting lymphoid neoplasia and warranted further specific and elaborate investigation.

The use of the historic kappa/lambda ratio by itself is not sensitive enough to detect a composite of 2 B-cell populations having different surface Ig light chains which largely depends on the population size and may be often within the normal range [17]. Therefore, more creative methodologies are used with proper analysis and interpretation of cell markers. The inclusion of immunostains with high specificity to one or each of the 2 B-cell neoplasms is a further adjunct to proper diagnosis. This was recently recommended by Sun et al. (2018) [13] who included LEF-1 immunostain in the workup given its overexpression in CLL/SLL with high specificity [18,19]. In our case, PB and bone marrow aspirate/biopsy cytologic and histologic examination were suggestive of CLL/SLL while a concurrent other lymphoid neoplasm was not suspected. The presence of composite lymphoma was identified exclusively with the aid of flow cytometry analysis that confidently detected the composite of 2 CD5+ve mature B-cell neoplasms having different light chain restriction. Differences in the antigen expression pattern was also helpful, in particular, dimmer CD20 together with the expression of CD23, CD43, CD200, and dimmer expression of CD79b on the kappa monotypic population (pattern characteristics for CLL/SLL). On the other hand, normal CD20 expression, negative for CD43 and CD200 together with the expression of FMC7 on the lambda-restricted monotypic cells clearly supported the presence of another CD5 positive B-cell neoplasm in addition to CLL/SLL. Although LEF-1 immunostain was not performed, the pattern of positivity for PAX5, CD20, and cyclin D1 immunostains was complementary to flow cytometry and supportive of a composite lymphoma.

Genetic analysis is an integral tool in the exhaustive yet successful multiparametric approach that can help resolve the diagnostic dilemma of composite lymphoma. In our case, FISH analysis successfully demonstrated IGH/CCND1 rearrangement, t(11;14), in 69% of cells analyzed and confirmed MCL.

Despite the fact that CLL/SLL and MCL share some morphologic and immunophenotypic features and are assumed to arise from mature CD5+ B-lymphocytes with mutated or unmutated IGHV genes, results from 4 case reports [8–11] and another 7 cases from the largest published series of 11 cases by Hoeller et al. (2013) [12] revealed absence of a clonal association in between these 2 B-cell neoplasms as indicated from the different immunophenotypic pattern or type of the light chain expression, t(11;14) and variable IG rearrangements (Supplementary Tables 1 and 2 summarize findings in previously reported cases). These findings support that CLL/SLL and MCL represent mutually exclusive lymphomagenic paths (naïve CD5+ B-cells; CLL/SLL is more related to apoptosis arrest and NF-kB activation, while MCL being strongly linked to dysregulation of cell cycle through cyclin D1 overexpression and DNA damage response pathway inactivation [12]. This finding is in line with the World Health Organization (WHO) classification that distinguishes these 2 neoplasms as separate lymphoma entities.

In the case reported hereby, the different antigens expression pattern by the 2 neoplasms together with different light chain restriction suggests unrelated clonality. However, this is not an absolute clue of different clonal origin as suggested by Wing et al. (2012) [20] who reported a case of concurrent plasmacytoma and B-cell lymphoma with different light chain restriction, but were found to be clonally related at molecular level using DNA from the plasmacytoma and micro-dissected lymphoma cells. Unfortunately, such sophisticated molecular tests were not available for this case.

There are still some unanswered questions. Is MCL and its occurrence as part of a composite lymphoid neoplasm like CLL/SLL a mere coincidence or rather a genomic evolution given the high degree of genomic instability characterizing MCL? Is there a common precursor B-cell that has undergone a multistep mutation which ended up with the development of these 2 neoplasms? Is this a microenvironment driven process? All these are still under debate and requires additional research and investigation.

Ancillary studies including flow cytometry, immunohistochemistry, cytogenetic and molecular testing should always be considered to unveil a possible concurrent neoplastic component. This is important for proper case diagnosis and management since multiple disease entities may not only have different natural history but may also differ in prognosis and treatment. Immunohistochemical
stains such as LEF-1 for detection of CLL/SLL cells and SOX-11, which may detect MCL including those cases without a cyclin D1 translocation may be useful in laboratories who do not have immediate access to other testing modalities such as flow cytometry, chromosomal, cytogenetics or molecular studies. Clinically, manifestation of CL is similar with that of ordinary lymphoma in general and there is no evidence that, when taking part in a composite, the clinical course differs significantly when considering the component with the poorest prognosis [14] on which therapeutic decision should always be based.

Conclusions

This is a report of composite lymphoma of MCL (small cell variant) and CLL/SLL emphasizing the vital role of multiparametric approach including vigilant cyto-histopathologic examination, immunophenotyping by flow cytometry and immunohistochemistry as well as genetic testing for the correct diagnosis and classification of lymphoid neoplasms. This importance is underscored in cases of small B-cell lymphoma to discern morphologically unrecognized concurrent MCL in cases of CLL/SLL and vice versa. A flow cytometry panel including CD19, CD79b, CD20, CD5, CD23, CD10, FMC7, CD43, and CD200 in addition to kappa and lambda light chains is helpful in distinguishing MCL from CLL/SLL and to peruse for further investigation for a correct diagnosis.

Conflict of interest

None.

Supplementary Data

Supplementary Table 1. Clinical, peripheral blood, bone marrow and lymph node findings in the reported cases.

| Ref # | No of cases | Sex/age (yr) | Blood findings | BM findings | BM infiltration pattern | LN findings | LN infiltration pattern | MCL morphology |
|-------|-------------|--------------|----------------|-------------|------------------------|-------------|------------------------|----------------|
| 8     | 1           | F/69         | CLL: Main clone MCL: Small clone | ND          | --                     | CLL and MCL | CLL: Diffuse MCL: Nodular | Medium size lymphocytes with irregular nucleus |
| 9     | 1           | M/86         | CLL: 90% MCL: 10% | CLL: 59% MCL: 27% | Nodular and interstitial | CLL: 10% MCL: 90% | NM | Large, less condensed chromatin, nucleoli |
| 10    | 1           | M.73         | CLL only | CLL only | Mild infiltration (15%) | CLL and MCL | Diffuse | Small lymphocytes |
| 11    | 1           | F/84         | CLL: 10% MCL: 30% | MCL & CLL | Nodular and interstitial | No LN | No LN | Small to medium lymphocytes |
| 12    | 7           | CLL/MCL     | M/6, F/1 55–80 | Not detailed | Not detailed | CLL: Not detailed MCL: Nodular (1/7)* | CLL and MCL (6/7) | CLL: Internodular (6/7) MCL: In situ (1), Mantle zone (1), Nodal and diffuse (1), diffuse (3) | Small lymphocytes (4), blastoid (3) |
| 12    | 4           | SLL/MCL     | Not detailed | M (4) 69–79 | Not detailed | SLL: Internodular (2), Diffuse (1), Nodal (1) MCL: Nodal and diffuse (2), Focal (1), Mantle zone (1) | Small lymphocytes (1), blastoid (3) |
| Current case | 1           | M/57        | CLL: 12% MCL: 58% | CLL: 10% MCL: 59% | MCL: Interstitial CLL: Nodular and interstitial | ND | ND | Small cell variant |

M – Male; F – Female; LN – lymph node; PB – peripheral blood; NM – not mentioned; ND – not done; CLL – chronic lymphocytic leukemia; MCL – mantle cell lymphoma; * One case with bone marrow involvement only.

Supplementary Table 1. Clinical, peripheral blood, bone marrow and lymph node findings in the reported cases.
### Supplementary Table 2. Immunophenotypic, cytogenetics/FISH, and clonal relationship findings in the reported cases.

| Ref # | Immunophenotype FCM/IHC | Light chain | Cytogenetic/FISH | Clonal relationship |
|-------|-------------------------|-------------|------------------|---------------------|
| 8     | CLL: CD5⁺, CD23⁺, CD20⁺, CD43⁺, IgD⁻/⁺<br> MCL: CD5⁻/⁺, CD23⁻, CD20⁻, cyclin D1⁻, IgD⁻ | CLL: Kappadim | ND | No clonal relationship (IgH gene molecular studies) |
|       |                         | MCL: Lambda |                 |                     |
| 9     | CLL: CD19⁺, CD22⁻/⁺, CD23⁻/⁺, CD25⁻/⁺, FMC7⁻, CD5⁻, CD10⁻, CD11a⁻, CD11c⁻, CD20⁻, CD38⁻, CD79b⁻, CD103⁻, sig⁻<br> MCL: CD19⁻/⁺, CD20-high, CD22-high, CD25-low, CD38-low, CD79b⁻, FMC7⁺, CD5⁺, CD10⁻, CD11a⁺, CD11c⁻, CD23⁻, CD103⁻, sig-high (IgM) | CLL: Negative | PB: t(11;14) in 9%. 13q14.3 deletion in 21%<br> LN: t(11;14) in 94% | No clonal relationship (IgH gene molecular studies) |
|       |                         | MCL: Kappa |                 |                     |
| 10    | CLL: CD19⁺, CD5⁻, CD23⁻ and FMC7⁻, weak CD79 & weak sig. cyclin D1⁻<br> MCL: CD20⁺, CD5⁺, CD23⁻, cyclin D1⁻ | CLL: NM | FISH on LN: Show t(11;14).<br> FISH on BL & BM: No translocation | No clonal relationship, t(11; 14) in MCL cells only (FISH on LN)) |
|       |                         | MCL NM |                 |                     |
| 11    | CLL: CD19⁺, CD20⁻/⁺, CD5⁺, CD22⁺, CD23⁻, CD10⁻ & FMC7⁻<br> MCL: CD19-high, CD20-high, CD5-high, CD22⁺, FMC7⁻, IgM⁺, CD10⁻ and CD23⁻ | CLL: Lambda-high | FISH on PB: t(11;14), 6q⁻, 11q-trisomy 12, 13q⁻, trisomy 17 | No clonal relationship (different monotypic light chain) |
|       |                         | MCL: Kappa |                 |                     |
| 12    | (7 cases)<br> CLL/MCL | CLL/MCL: Kappa (1)<br> CLL/MCL: Lambda (1)<br> CLL/MCL: Lambda (3), Kappa (1), ND (1)<br> CLL/MCL: Lambda (3), Kappa (3), ND (1) | CLL: No t(11;14) | No clonal relationship (IgH gene molecular studies) |
| (4 cases)<br> SLL/MCL | SLL: CD5⁺, CD20⁺, CD23⁺, cyclin D1⁻<br> MCL: CD5⁺, CD20⁺, CD23⁺, cyclin D1⁻ | SLL: Lambda (3), Not done (1)<br> MCL: Lambda (3), ND (1) | SLL: No t(11;14) | No clonal relationship (IgH gene molecular studies) |
| Current Case | CLL: CD19⁺, CD23⁺, CD5⁺, CD43⁺, CD200⁻, CD38⁻, cBCL2⁻, IgD⁺, IgM⁺, CD79b⁻/⁺, CD20, cyclin D1⁻<br> MCL: CD19⁺, CD79b⁺, CD20⁺, CD5⁺, FMC7⁻, cBCL2⁻, IgD⁺, IgM⁺, CD23-partial, cyclin D1⁻ | CLL: Kappa | PB: t(11;14), in 65% of cells | No clonal relationship (different monotypic light chain) |
|       |                         | MCL: Lambda |                 |                     |

PB – peripheral blood; NM – not mentioned; ND – not done; FCM – flow cytometry; IHC – immunohistochemistry; FISH – fluorescence in situ hybridization; CLL – chronic lymphocytic leukemia; MCL – mantle cell lymphoma; SLL – small lymphocytic lymphoma; LN – lymph node; BM – bone marrow.
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