Lymphoplasmacytic lymphoma and a CD5+ lymphoproliferative process presenting as composite disease in the bone marrow: a report of two cases

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Abstract

Correct subclassification of B cell lymphoma requires integration of histologic and immunohistochemical findings in addition to results of flow cytometric immunophenotyping, cytogenetic analysis, and molecular studies. Evaluation for the MYD88 L265P mutation and immunohistochemical staining for LEF1 can be helpful in the workup of small B cell lymphomas. In this case report of two diagnostically difficult cases, we present two patients with lymphoplasmacytic lymphoma (LPL) and a CD5+ lymphoproliferative process presenting as composite disease within the bone marrow. In both cases, integration of ancillary studies and results of biopsy at other sites of disease in addition to a careful histologic review and an expanded immunohistochemistry panel were important for the correct final classification.

Keywords Chronic lymphocytic leukemia · Small lymphocytic lymphoma · Lymphoplasmacytic lymphoma · Composite

Introduction

Hematoxylin and eosin (H&E) morphology, immunohistochemical stains, flow cytometric immunophenotyping, ancillary studies including cytogenetic and molecular studies, and clinical features are all used to subclassify B cell lymphomas according to the revised 4th edition of the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues [1]. Evaluation for the MYD88 L265P mutation has become a standard ancillary study in the diagnosis of lymphoplasmacytic lymphoma (LPL); however, the presence of the mutation is not entirely specific [2]. For example, in various studies, 2–5% of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) cases had the MYD88 L265P mutation. Immunohistochemical staining for lymphoid enhancer binding factor 1 (LEF1) is helpful in

the diagnosis of CLL/SLL, being aberrantly expressed in nearly all cases of CLL/SLL [3]. The subclassification of small B cell lymphomas is not always straightforward, and there can be overlap in features among the different subtypes. Rarely, a composite lymphoma consisting of two or more morphologically and immunophenotypically distinct lymphoma clones in a single anatomic site occurs. In contrast to composite lymphomas comprised of a low-grade B cell lymphoma and an aggressive B cell lymphoma or Hodgkin lymphoma, which are usually clonally related, there is evidence that composite lymphomas consisting of two indolent B cell lymphomas are biclonal [4–6].

In this report, we present two diagnostically difficult cases of LPL and a CD5+ lymphoproliferative process of CLL/SLL type presenting as composite disease within the bone marrow.

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Clinical history

Case 1

A 65-year-old male, who was otherwise healthy without any medical problems, presented with a dental abscess that required tooth extraction and prolonged course of antibiotics. He was found to have a protein gap with total protein 9.8 g/dL

and albumin 3.2 g/dL and a new mild anemia with hemoglobin 11.7 g/dL. Serum protein electrophoresis and immunofixation (SPEP/IFIX) revealed an IgM kappa monoclonal protein (3.2 g/dL), total IgM 3978 with concurrent immunoparesis. Serum free light chains were elevated with a kappa to lambda free light chain ratio of 8:1. No bone abnormalities were seen by skeletal survey, and no cervical, supraclavicular, axillary, or inguinal adenopathy was noted on physical exam. A bone marrow biopsy was performed, and CT scans were obtained.

Case 2

A 76-year-old male with new renal insufficiency (GFR 30–59 mL/min, stage 3) was found to have a normocytic normochromic anemia and IgM kappa serum protein (0.8 g/dL) with elevated free kappa light chains. The peripheral blood showed slight anemia (hemoglobin 12.5 g/dL) and a leukocyte count at the high end of normal (10.5 K/ μ L) with an absolute lymphocyte count of 3.6 K/ μ L. A bone marrow biopsy was performed.

Materials and methods

The cases were identified during routine clinical practice. The electronic medical record was used to extract clinical information including patient age, gender, medical history, staging, treatment, and follow-up. H&E-stained slides, immunohistochemically stained slides, Wright–Giemsa–stained aspirate smears, and peripheral blood smears were prepared according to routine protocols in place at the time of diagnosis. Flow cytometry was performed by 8-color analysis or 6-color analysis on a FACSCanto II flow cytometer (Becton Dickinson, San Jose, CA) using routine protocols in place at the time of diagnosis. Cytogenetic studies including karyotype and fluorescence in situ hybridization (FISH) and molecular analysis were performed using routine protocols in place at the time of diagnosis.

Results

Clinicopathologic features of the two cases are summarized in Table 1.

Case 1

The Wright–Giemsa–stained aspirate smear showed increased monotonous lymphocytes (29% on differential count), increased plasma cells (7%), and frequent mast cells (see Fig. 1). H&E-stained sections of the core biopsy showed a dense interstitial lymphoplasmacytic infiltrate with frequent mast cells. By immunohistochemical stains, the

lymphoplasmacytic infiltrate was predominantly comprised of CD20-positive B cells negative for CD5, CD10, and LEF1, and frequent CD138-positive plasma cells; the infiltrate comprised an estimated 40–50% of the marrow. By chromogenic in situ hybridization for kappa and lambda immunoglobulin light chains, the lymphoplasmacytic infiltrate was kappa restricted. There were also occasional distinct lymphoid aggregates present, comprising an estimated 5% of the marrow, best seen on immunohistochemically stained slides, positive for CD5, PAX5, and LEF1 but negative for CD3 and CD20. Flow cytometry performed on the marrow aspirate identified two distinct kappa monotypic B cell populations, one positive for CD5 and CD23 but lacking FMC7 (29% of lymphocytes), and one negative for CD5 and CD23, with variable FMC7 expression (12% of lymphocytes) (see Fig. 2). In addition, there were rare plasma cells identified by CD138 and bright CD38 positivity. The plasma cells lacked CD56 and CD117; however, there were too few plasma cells to definitively evaluate for light chain restriction. Allele-specific polymerase chain reaction (PCR) performed on a bone marrow aspirate specimen was positive for the MYD88 L265P alteration as well as the following pathogenic mutation in CXCR4: g.136872485G>C; c.1013C>G. Karyotype showed loss of the Y chromosome in 4 metaphases with the remaining 16 metaphases showing a normal 46,XY karyotype. An enrichment process for CD138-positive cells was performed and yielded only enough interphase nuclei to run one FISH, with the TP53/CEP17 probe set showing a normal signal pattern. Additional FISH analysis using the CLL panel of probes (MYB[6q23.3], ATM[11q22.3]/TP53[17p13.1], CCND1/IGH t[11;14], and CEP12/13q14.3/13q34 probe sets) on nuclei from the culture of bone marrow sample showed signal patterns consistent with normal controls. Evaluation for IGH somatic hypermutation performed on the bone marrow sample identified two functional IGH V rearrangements, one mutated and one un-mutated.

Computed tomography imaging performed as part of the initial workup of the IgM monoclonal protein demonstrated enlarged mesenteric and retroperitoneal lymph nodes, with the largest conglomerate measuring up to 13.3 × 6 cm in largest dimension. Ultrasound-guided core needle biopsies of the mesenteric mass were obtained with morphology and immunohistochemistry diagnostic of chronic lymphocytic leukemia/small lymphocytic lymphoma (Fig. 3). Flow cytometry identified a CD5-positive cytoplasmic kappa monotypic B cell population positive for CD5, CD23, and CD19 but lacking CD10, CD20, FMC7, and surface light chain expression. Pyrosequencing targeting codon 265 of the MYD88 gene was performed on the formalin-fixed paraffin-embedded tissue from the mesenteric mass biopsy, with no mutation detected. Flow cytometry of the peripheral blood to assess for circulating lymphoma cells identified only a minute population of B cells, of insufficient size to evaluate for light chain restriction.

Table 1 Clinicopathologic features of the two cases

Case	Age, gender	Bone marrow diagnosis	Bone marrow flow cytometry	Extramedullary biopsy site diagnosis	SPEP/IFIX	Lymphadenopathy/splenomegaly	MYD88 L265P mutation status	Cytogenetics
1	65, M	1. Lymphoplasmacytic lymphoma (40–50% of marrow) 2. Focal marrow involvement by SLL/CLL (~ 5% of marrow)	Pop 1 (29% of lymphocytes): CD5+CD23+ FMC7-kappa monotypic B cells. Pop 2 (12% of lymphocytes): CD5-CD10-kappa monotypic B cells. Pop 3: rare plasma cells lacking CD117 and CD56 (light chain expression could not be assessed).	SLL (mesenteric mass/lymph node)	IgM kappa (3.2 g/dL)	Mesenteric and retroperitoneal up to 13.3 cm/mild splenomegaly	Bone marrow aspirate: positive. Mesenteric mass biopsy: negative.	Bone marrow FISH: normal results for the following probes: del6q (MYB), t(11;14)(CCND1/IGH), ATM(11Q22)/TP53(17P13.1), CEP12/13Q14.3/13Q34.
2	76, M	1. Lymphoplasmacytic lymphoma (20–30% of marrow) 2. Monoclonal B cell lymphoproliferative process (identified by flow cytometry but not histology)	Pop 1 (23% of lymphocytes): CD5+ CD20(dim+), CD23+CD79b-, dim surface kappa monotypic B cells. Pop 2 (3% of lymphocytes): CD5-CD20(dim+)CD23-, bright surface kappa monotypic B cells Pop 3: rare kappa monotypic plasma cells lacking CD56	Involvement by LPL (kidney)	IgM kappa (0.8 g/dL)	Retroperitoneal and porta hepatis up to 2.5 cm/no splenomegaly	Bone marrow aspirate: 1% VAF, 2% VAF (on repeat) DNA isolated from cell pellet for FISH analysis: 0% VAF Kidney biopsy: not performed	Bone marrow FISH: loss of the 13q14.2 region (23% interphase cells)

SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; *SPEP/IFIX*, serum protein electrophoresis and immunofixation; *LPL*, lymphoplasmacytic lymphoma

On initial review of the bone marrow biopsy, the specimen was interpreted as a small B cell lymphoma with plasmacytic differentiation, with a CD5-positive lymphoplasmacytic lymphoma leading the differential. After the subsequent mesenteric mass biopsy obtained 2 weeks later, additional immunohistochemical stains on the bone marrow core identified the CD20-negative, Pax5- and LEF1-positive lymphoid aggregates. The final interpretation of the bone marrow in case 1 was marrow involvement by lymphoplasmacytic lymphoma in addition to focal marrow involvement by SLL/CLL. The patient was started on ibrutinib and obinutuzumab.

Interim CT scans after three cycles of treatment showed a partial response with a decrease in the anterior mesenteric mass to 6×1.8 cm, and near complete resolution after six cycles. Though his scans demonstrated an excellent response to therapy, his IgM levels have remained elevated and have shown a more gradual decline. At therapy initiation, total protein had reached 10.5 g/dL, IgM kappa M-spike 3.35 g/dL, IgM 5744, and K:L ratio 14.61. Protein studies after 4 months of therapy showed some improvement with total protein 9.7 g/dL, IgM kappa M-spike 2.51 g/dL, IgM 4925, and K:L ratio 11.58. After six cycles of ibrutinib with

Fig. 1 Case 1 bone marrow findings. H&E-stained sections of the core biopsy show a dense lymphoplasmacytic infiltrate with frequent mast cells (black star) (a, b, 40× objective). The Wright–Giemsa-stained aspirate smear shows increased monotonous lymphocytes, increased plasma cells, and frequent mast cells (black arrow) (c, 100× oil objective). The interstitial lymphoplasmacytic infiltrate is highlighted by CD20 and CD138 immunohistochemical stains on the core biopsy (d, e, respectively, 20× objective). In addition to the interstitial infiltrate, occasional lymphoid aggregates were present, best seen on immunohistochemically stained slides. Panel f shows the staining pattern of a representative lymphoid aggregate, positive for CD5, Pax5 (not shown), and LEF1 and negative for CD3 and CD20 (all 20× objective). There are background T cells by CD3

obinutuzumab, he was switched to ibrutinib monotherapy. He feels very well on therapy with normalization of his hemoglobin to 14.7 g/dL and a continued gradual improvement in his protein gap with total protein 9.4 g/dL and albumin 4.3 g/dL.

Case 2

The Wright–Giemsa-stained aspirate smear showed a paucicellular and hemodilute specimen, while the Wright–Giemsa-stained touch imprint was representative of the

Fig. 2 Case 1 bone marrow flow cytometry findings. Flow cytometry of the bone marrow aspirate identified a CD5-positive kappa monotypic B cell population positive for CD23 and lacking FMC7 (green). Also

present was a CD5-negative kappa monotypic B cell population with slightly brighter surface kappa expression, lacking CD23, and with variable FMC7 expression (red)

Fig. 3 Case 1 lymph node findings. **a** H&E-stained sections from a needle core biopsy of the mesenteric mass/lymph node showed a vaguely nodular atypical lymphoid infiltrate comprised of small monotonous appearing lymphocytes with interspersed proliferation centers (40× objective). Immunohistochemical staining showed the population of interest to be positive for CD19, CD5, and LEF1 (**b–d**, 20× objective). Not shown, the atypical lymphocytes were positive for Pax5, predominantly negative for CD20, and negative for CD10 and cyclinD1

marrow showing frequent atypical lymphocytes, lymphoplasmacytic cells, and occasional plasma cells (Fig. 4). H&E-stained sections from the bone marrow core biopsy showed paratrabecular lymphoid aggregates, comprising an estimated 20–30% of the marrow, comprised of small lymphoplasmacytic cells, including forms with nuclear pseudo-inclusions (Dutcher bodies) and frequent interspersed mast cells. By immunohistochemical stains, the lymphoid aggregates were comprised predominantly of CD20-positive B cells negative for CD5, CD10, CD23, and LEF1. Flow cytometry performed on the hemodilute aspirate specimen demonstrated two abnormal B cell populations and a monotypic plasma cell population (Fig. 5). A CD5-positive B cell population with dim surface monotypic kappa staining was identified (25% of lymphocytes) in addition to a distinct CD5-negative B cell population with bright surface monotypic kappa staining (3% of lymphocytes). There were also rare kappa monotypic plasma cells negative for CD56 with positive CD19 and fairly bright CD45 (similar to lymphocytes). FISH performed on the bone marrow aspirate showed homozygous loss of D13S319 in 23% of interphase cells consistent with homozygous loss of the 13q14.2 region. Signal patterns for MYB(6q23.3), CCND1/IGH t(11;14), ATM(11q22.3), CEP12, TP53(17p13.1), and BCL2(18q21) break apart probe sets were consistent with normal controls. Next-generation sequencing extended analysis was performed twice on the bone marrow aspirate as well as on DNA isolated from the cell pellet used for FISH analysis. The analysis on the bone marrow aspirate provided sub-threshold evidence for the presence of L265P mutation in MYD88 at variant allele frequencies (VAF) of 1% and 2%. The L265P mutation in MYD88 was not detected in DNA isolated from the cell pellet used for

FISH analysis (0% VAF). In summary, the hemodilute aspirate appears to contain a sizeable population of CLL/SLL-like B cells positive for CD5 and CD23 with 13q14.2 loss by FISH with only a small second population of CD5-negative kappa monotypic B cells and rare kappa monotypic plasma cells corresponding to the LPL infiltrates seen in the core biopsy.

Subsequent CT scan identified retroperitoneal and porta hepatis lymphadenopathy up to 2.5 cm in greatest dimension. The spleen was of normal size. One month after bone marrow biopsy, a renal biopsy was performed for progressive renal failure. Renal biopsy findings (Fig. 4g, h) consisted of moderate advanced diabetic nephropathy and nodular glomerulosclerosis, acute tubular epithelial injury, and an atypical lymphoid infiltrate expanding the interstitium. By immunohistochemical stains, the atypical lymphoid infiltrate was positive for CD20 and negative for CD5, CD23, and LEF1. Kappa monotypic plasma cells were present by kappa and lambda in situ hybridization. Neither flow cytometry nor molecular diagnostics for MYD88 were performed on the renal biopsy.

The findings in case 2 were interpreted as lymphoplasmacytic lymphoma involving the bone marrow and kidney, with concurrent CD5-positive B cell lymphoproliferative processes identified in the bone marrow aspirate specimen by flow cytometry with supportive findings by FISH (13q14.2 loss), representing monoclonal B cell lymphocytosis of CLL-type. A definitive morphologic correlate to the CD5-positive B cell lymphoproliferative process identified by flow cytometry was not seen in the marrow histologic sections and is hypothesized to represent peripheral blood contamination of the marrow aspirate sample. The patient was started on ibrutinib which was discontinued after 1 month of therapy due

Fig. 4 Case 2 bone marrow biopsy and kidney biopsy findings. The Wright–Giemsa–stained aspirate smear shows a paucicellular and hemodilute specimen (**a**, 20× objective), while the Wright–Giemsa–stained touch imprint is representative of the marrow and shows frequent atypical lymphocytes, lymphoplasmacytic cells, and occasional plasma cells (**b**, 100× oil objective). H&E–stained sections from the bone marrow core biopsy show paratrabeular lymphoid aggregates comprised of small lymphoplasmacytic cells, including forms with nuclear pseudo-inclusions (Dutcher bodies) and frequent interspersed mast cells (**c**, 40× objective). The paratrabeular lymphoid aggregates are seen on low-power view of the H&E–stained core biopsy (**d**, 10× objective); the lymphoid aggregates are predominantly B cells (**e**, CD20 immunohistochemical stain, 20× objective), with kappa restriction by immunohistochemical stains for kappa and lambda (**f**, 20× objective). There were scattered plasma cells, including at the periphery of the lymphoid aggregates. Renal biopsy findings included an atypical lymphoid infiltrate expanding the interstitium (**g**, 20× objective). By immunohistochemical stains, the infiltrate is positive for CD20 and negative for LEF1 (**h**, 20× objective)

to rising creatinine level. Over the next 3 months, the leukocyte counts oscillated near the upper range of normal and hemoglobin trended down, with a nadir of 9.9 g/dL. He developed encephalopathy with altered mental status and progressive loss of vision; there were no acute changes on brain imaging. The patient showed progressive renal failure which was felt to be due to mixed etiology including diabetes mellitus, hypertension, and the lymphoplasmacytic lymphoma with monoclonal protein. The patient received rituximab twice and had a trial of plasmapheresis without clear clinical benefit. The encephalopathy was considered most likely due to long-term complications of diabetes and hypertension instead of viscosity as the IgM protein level was less than 1

g/dL. The patient was transferred to hospice care and died 6 months after initial bone marrow biopsy.

Discussion

In this paper, we describe two diagnostically challenging cases of indolent B cell lymphoma presenting in the bone marrow. The final interpretation of the bone marrow in case 1 was marrow involvement by lymphoplasmacytic lymphoma in addition to focal marrow involvement by SLL/CLL. We feel that this represents a true composite lymphoma consisting of two morphologically and immunophenotypically distinct lymphoma clones in a single anatomic site. While we did not perform microdissection

Fig. 5 Case 2 bone marrow flow cytometry findings. Flow cytometry on the aspirate specimen demonstrated two abnormal B cell populations and a monotypic plasma cell population. A CD5-positive CD19-positive B cell population with expression of CD20 (dim) and CD23 and dim surface kappa monotypic immunoglobulin light chain staining was identified comprising 25% of the lymphocytes (green population). In addition, there

was a distinct kappa monotypic B cell population with dim CD20 expression and bright surface kappa monotypic light chain staining but negative for CD5 and CD23 comprising 3% of the lymphocytes (blue population). There were also rare kappa monotypic plasma cells negative for CD56 with positive CD19 and fairly bright CD45 (similar to lymphocytes) (not shown)

of the bone marrow biopsy to separate the two immunophenotypically distinct lymphoma populations, the presence of an MYD88 mutation in the bone marrow aspirate specimen and lack of an MYD88 mutation in the mesenteric mass/lymph node biopsy are supportive of two separate clonal processes. In addition, while the presence of two functional IGH V rearrangements in the bone marrow could represent bi-allelic rearrangement of IgH, it is also consistent with the presence of a two separate clonal B cell populations. The immunohistochemical features of the SLL in the mesenteric mass corresponded exactly with those of the small lymphoid nodules in the marrow including CD20 negativity and LEF1 positivity. The final interpretation of case 2 was lymphoplasmacytic lymphoma involving the bone marrow with a concurrent CD5-positive monoclonal B cell lymphocytosis identified by flow cytometry. In case 2, the pairing of sub-threshold evidence of the MYD88 mutation in the hemodilute marrow aspirate sample but lack of detection of the MYD88 mutation in the cell pellet used for FISH analysis (which showed the common CLL cytogenetic finding of loss of the 13q14.2 region) in conjunction with the immunophenotypically

distinct populations on flow cytometry is supportive of two separate clonal processes. Our data is in line with evidence in the literature that composite lymphomas consisting of two indolent B cell lymphomas tend to be biclonal [4–6]. Composite cases of LPL and CLL/monoclonal B cell lymphocytosis have been rarely described in the literature, with subtyping of the populations by MYD88 genotyping performed in two case reports [7, 8].

Recognizing such composite lymphoproliferative processes requires vigilance on the part of the sign-out pathologist. Careful review of the flow cytometry plots for B cell populations with distinct immunophenotypic profiles is key; such evaluation is aided by multiparametric flow cytometric evaluation using 8–10 colors. A full immunohistochemical panel is also important. Multiple B cell markers may be needed in scenarios of CLL with weak to negative CD20 expression. CD5 and LEF1 are helpful when interpreted in conjunction with CD3. LEF1 shows relatively high specificity for CLL/SLL, including in the context of CD5-positive small B cell lymphomas [9–11]. CD5 positivity in lymphoplasmacytic lymphoma is identified in a minority of cases [12, 13], and CLL/SLL with plasmacytic differentiation has been

rarely reported [14], highlighting the need for incorporation of all available data before establishing a diagnosis. Correlation with results of FISH studies and molecular testing is vital as is awareness on the part of the pathologist of any additional biopsies or studies performed. The MYD88 L265P mutation is neither entirely sensitive nor specific for lymphoplasmacytic lymphoma. MYD88 mutations have been identified in chronic lymphocytic leukemia in 2–5% of cases in various studies [2, 15, 16].

Our aim with this paper is to raise the pathologist's awareness of composite lymphomas identified in the bone marrow comprised of lymphoplasmacytic lymphoma with a concurrent CD5-positive lymphoproliferative processes. Recognition of such composite or potentially composite lymphomas may prompt additional workup or biopsy of additional sites of disease by the clinical team and may aid in disease monitoring during therapy. Correlation of histology, immunohistochemistry, flow cytometric immunophenotyping, ancillary studies including cytogenetic and molecular studies, and clinical features are all important.

Data availability Not applicable.

Compliance with ethical standards

Conflict of interest Not applicable.

Ethics approval IRB approval is not required for case reports by institutional policy.

Consent to participate Not applicable.

Code availability Not applicable.

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