Concurrent Waldenstrom’s Macroglobulinemia and Myelodysplastic Syndrome with a Sequent t(10;13)(p13;q22) Translocation

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Abstract: Myelodysplastic syndromes (MDS) and Waldenstrom’s macroglobulinemia (WM) are rarely synchronous. Ineffective myelopoiesis/hematopoiesis with clonal unilineage or multilineage dysplasia and cytopenias characterize MDS. Despite a myeloid origin, MDS can sometimes lead to decreased production, abnormal apoptosis or dysmaturaion of B cells, and the development of lymphoma. WM includes bone marrow involvement by lymphoplasmacytic lymphoma (LPL) secreting monoclonal immunoglobulin M (IgM) with somatic mutation (L265P) of myeloid differentiation primary response 88 gene (MYD88) in 80–90%, or various mutations of C-terminal domain of the C-X-C chemokine receptor type 4 (CXCR4) gene in 20–40% of cases. A unique, progressive case of concurrent MDS and WM with several somatic mutations (some unreported before) and a novel balanced reciprocal translocation between chromosomes 10 and 13 is presented below.

Keywords: hematology/oncology; cytogenetics; lymphoma; myelodysplastic syndrome; pathology; genetics

1. Introduction
Myelodysplastic syndromes (MDS) and Waldenstrom’s macroglobulinemia (WM) are rarely synchronous. MDS is characterized by an ineffective myelopoiesis/hematopoiesis with clonal unilineage or multilineage dysplasia and cytopenias. WM includes bone marrow involvement by lymphoplasmacytic lymphoma (LPL) secreting monoclonal immunoglobulin M (IgM) with somatic mutation (L265P) of myeloid differentiation primary response 88 gene (MYD88) in 80–90%. We present a case of concurrent MDS and WM, with a unique translocation and somatic mutations.

2. Case
A 71-year-old, previously healthy, African American, male, landscaper, presented in 2014 with a 2 month history of shortness of breath, intermittent light-headedness, and fatigue. Work up detected normocytic anemia (hemoglobin (Hgb) = 6.1 g/dL), thrombocytopenia, (platelets (Ptl) = 111 × 10^3/µL), proteinemia (IgM = 1140 mg/dL), and monoclonal gammopathy (IgM Kappa = 0.43 g/dL). White blood cell count (WBC = 3.8 × 10^3/µL), urine protein electrophoresis, serum free light chain studies, and bleeding/hemolytic
workup were normal. A bone marrow (BM) biopsy (Figure 1) showed hypercellularity for age (95%), erythroid hyperplasia (myeloid:erythroid ratio of 1:3) with megaloblastic changes, mild left shift, megakaryocytic dysplasia with clustering and <5% blasts. A diffuse interstitial lymphoid infiltrate composed mostly of small, mature lymphocytes with plasmacytic differentiation (lymphoplasmacytes) representing approximately 30% of cellularity was noted. Diffuse moderate reticulin fibrosis (grade 1–2 on a 0–3 scale) was present (Figure 1). Flow cytometry analysis (including plasma cell and paroxysmal nocturnal hemoglobinuria panels) showed no immunophenotypic abnormalities due to aspirate sampling variation. Immunohistochemistry (IHC) revealed monoclonal, kappa-restricted lymphoplasmacytes positive for CD20, CD45, Pax5 (variably) and CD138; and negative for lambda, CD5 and CD10 (Figures 1 and 2). CD34 stained rare scattered blasts. Glycophorin A and myeloperoxidase confirmed erythroid hyperplasia.

**Figure 1.** Initial diagnostic bone marrow biopsy and aspirate. The marrow is markedly hypercellular with diffuse lymphoid infiltrates consisting of predominant small lymphocytes, plasmacytic lymphocytes and rare plasma cells (H&E at 20× and 400×, respectively, in (A) and (B)). In the background, there is maturing trilineage hematopoiesis with dysmegakaryopoiesis and few blasts ((C). H and E at 1000×) and erythroid hyperplasia with dysplasia ((D) Wright-Giemsa stained aspirate at 1000×). (Scale bars = 2 mm in magnification at 20×, 50 µm at 400×, and 25 µm at magnification 1000×).

Cytogenetic analysis demonstrated a normal 46XY karyotype. PCR was negative for JAK-2 (V617F and exons 12/13), MPL (W515 AND S505), CAL-R, MYD88, CXCR-4 and BCR/ABL mutations. Fluorescent in situ hybridization analysis was negative for deletions of 5q, 7q and 20q, monosomies of chromosomes 5 and 7, trisomy of chromosome 8, and for common aberrations associated with chronic lymphocytic leukemia or multiple myeloma. Therefore, the diagnoses of low-grade B cell lymphoproliferative disorder with plasmacytic differentiation, consistent with lymphoplasmacytic lymphoma (LPL) and a concomitant myeloid neoplasm compatible with low grade MDS were made.

Lenalidomide (10 mg for 21/28 days) was started per patient’s request to avoid parenteral hypomethylating agents, and transfusion independence was achieved for 1 year (until April 2015). Afterward, pancytopenia (WBC = 2.7 × 10^3/µL, Hgb = 7 g/dL, MCV = 75 fL, Plt = 32 × 10^9/L) and WM (M spike = 0.53 g/dL and IgM = 1500 mg) recurred. The pa-
tient received supportive treatment with blood product transfusions and eltrombopag prior to being scheduled for a BM transplant and receiving azacytidine for pre-transplant cytoreduction. A repeat BM biopsy (August 2015) showed residual LPL with normal cytogenetics. Hemolytic workup was negative, and also demonstrated hyperproteineemia (total protein = 8.6 g/dL) with an M-spike of 1.5 g/dL and total IgM of 2.86 g/dL indicating progression of WM.

Figure 2. Immunohistochemistry of the initial bone marrow biopsy showing the lymphoplasmacytic lymphoma to be positive for Pax5 (A) and negative for CD5 (B) with a plasmacytic component negative for kappa (C) and positive for lambda (D). (Scale bars = 50 µm at magnification 400×).

Azacytidine was stopped after 2 cycles given the development of pancytopenia secondary to WM progression in the setting of treatment with 2 doses of IVIG and 4 cycles of rituximab. The patient received maintenance rituximab therapy from 2015 to 2018 before being transitioned to ibrutinib and obinotuzumab in August, 2018, due to disease progression. This treatment regimen achieved IgM normalization prior to being discontinued in March 2019 due to persistent pancytopenia and an M spike surge.

A new BM biopsy (March 2019) revealed increased cellularity (90%) with residual low burden LPL, marked megakaryocytic hypoplasia, moderate residual reticulin fibrosis and an impressive reactive T cell infiltrate (confirmed by a negative T cell receptor rearrangement by PCR). Chromosomal analysis showed a new 20(q11.2q13.1) deletion supporting the diagnosis of residual MDS. NGS (Foundation Medicine) revealed PTEN G132D, B2M L15fs*41, CD58 S212*, CXCR4 Q318*, FOXP1 A100fs*50, POT1 N514fs*7, TNFAIP3 splice site 296-2A>G and R183* and PTEN G132D, B2M L15fs*41, CD58 S212*, CXCR4 Q318*, FOXP1 A100fs*50, POT1 N514fs*7, TNFAIP3 splice site 296-2A>G and R183* and CXCR Q318*. In addition, several additional variants of uncertain significance were reported: BRCA2 D1923A and R2502C, CSF1R L125M, EGFR T384S, E300 M2130f, ERBB4 V486L, FAS D265E, FAM46C L117_E122-WQEVQK, FBXO11 V545L, FGF23 P195S, HIST1H1E I80M, KMT2A (MLL) R2194H, LRP1B G1691V, MLL2 Q3867K, PAG1 T404S, PDCD1 (PD-1) A263T, PLCG2 E480K, SMARCA1 R259G, TBL1XR1 H441R and V210L, TLL2 R657W and ZNF217 A802T. All mutations were predicted as somatic based on frequency, loss of heterozygosity and copy number.

In August 2019, one cycle of dose-reduced bendamustine (30 mg/m²) and rituximab was administered, achieving improvement in blood transfusion requirements and undetectable M component. Figure 3 provides an outline of the patient’s treatment. However, severe pancytopenia (WBC = 0.5, Hgb = 8 and Pts = 20) persisted. A pre-BMT BM biopsy
(November 2019) showed decreased cellularity (50%) mostly composed of reactive T cells, stable moderate reticulin fibrosis and no residual lymphoma. Corresponding cytogenetics showed a novel t(10;13)(p13;q22) translocation. In addition, several additional alter-ations and precision medicine was not attempted since the patient expired. However, severe pancytopenia persisted (despite 60 units of pRBCs and 20 units of Plts) and the patient developed respiratory failure requiring intubation. A transtracheal aspirate culture revealed methicillin-resistant staphylococcus aureus and he ultimately expired. The autopsy showed marked multisystemic hemosiderosis involving liver, spleen, pancreas, adrenal glands, thyroid and lymph nodes. Post mortem BM biopsy showed marked aplasia without myelofibrosis or residual LPL. The cause of death was sepsis and iron overload.

3. Discussion

Herein, we presented a complicated case of simultaneous MDS and WM in a 71-year-old African American male, which required multiple therapies during a 6-year prolonged course. LPL and MDS were refractory to initial lenalidomide treatment. Diverse therapeutic strategies, including ibrutinib and obinutuzumab finally achieved WM remission; however, refractory MDS persisted and a 20(q11.2q13.1) deletion was detected 4 years after treatment. The deletion of the long arm of chromosome 20, or del(20q), is a common cytogenetic abnormality in various myeloid disorders, such as primary MDS (and less frequently secondary MDS) [1–3], but is less common in lymphoid neoplasms, including WM [4–8]. Therefore, the observed del(20q) may represent primary de novo MDS and/or LPL, or a secondary therapy-related malignancy.

NGS revealed many mutations potentially representing novel therapeutic targets involving various signaling cascades: NFkB-related cell proliferation/survival (CXCR4, TBL1XR1 and TLL2); PI3K/AKT/mTOR-induced protein synthesis/cell growth (CXCR4, CSF1R, EGFR, ERBB4, FGFR2, FOXP1, LRP1B, PTEN, PLCG2, SMARCA1 and TNAIP3), apoptosis regulation (B2M, FAS, FBXO11, PDCD1/PD-1 and ZNF217); maintenance of genomic stability/chromatin remodeling (BRCA2, EP300, HIST1H1E, MLL1, ML2, POT1, and SMARCA1); and evasion of antineoplastic immune responses (CD58). Interestingly at least fifteen novel alterations (CXCR4 Q318*, ERBB4 V486L, FAS D265E, FAM46C L117_E122>WQEVQK, FBXO11 V545L, FOXP1 A100fs*50, LRP1B G1691V, MLL/KMT2A R2194H, ML2 Q3867K, PDCD1 (PD-1) A263T, POT1 N514fs*7, SMARCA1 R259G, TNFAIP3 splice site 296-2A>G, TLL2 R657W and ZNF217 A802T) were discovered, which may inform the complex pathogenesis of this combined malignancy or represent therapy-related secondary hits [9].

Mutations in many of these genes have been shown to be pathogenic either in WM (B2M, CXCR4, EP300, FAM46C, FOXP1, HIST1H1E, LRP1B, MLL, ML2, PLCG2, PTEN, TBL1XR1 and TNAIP3) or MDS (BRC2, CSF1R, EGFR, EP300, FAS, FOXP1, MLL, ML2, PLCG2, PTEN, POT1 and PTEN) [1,3,10–15], while the rest have not been reported in association with WM (BRC2, CD58, ERBB4, FAS, FBXO11, FGFR2, PAG1, PDCD1, POT1 SMARCA1, TLL2 and ZNF217) or MDS (B2M, CD58, CXCR4, ERBB4, FAM46C, FBXO11, FGFR2, HIST1H1E, PAG1, PDCD1, SMARCA1, TBL1XR1, TLL2, TNFAIP3 and ZNF217) yet.

Well-known druggable oncogenic targets were PTEN, CXCR4, MLL2 and BRC2 [1,3,14,16]. However, further studies are necessary to fully understand the significance of these alterations and precision medicine was not attempted since the patient expired.

![Figure 3](https://example.com/fig3.png)

**Figure 3.** Treatment timeline during patient’s clinical course.

In January of 2020, the patient was hospitalized in preparation for an allogeneic BMT. However, severe pancytopenia persisted (despite 60 units of pRBCs and 20 units of Plts) and the patient developed respiratory failure requiring intubation. A transtracheal aspirate culture revealed methicillin-resistant staphylococcus aureus and he ultimately expired. The autopsy showed marked multisystemic hemosiderosis involving liver, spleen, pancreas, adrenal glands, thyroid and lymph nodes. Post mortem BM biopsy showed marked aplasia without myelofibrosis or residual LPL. The cause of death was sepsis and iron overload.

Well-known druggable oncogenic targets were PTEN, CXCR4, MLL2 and BRC2 [1,3,14,16]. However, further studies are necessary to fully understand the significance of these alterations and precision medicine was not attempted since the patient expired.
PTEN loss has been found in 3% of diffuse large B cell lymphomas but has not been reported in WM [17,18]. Although the PTEN G132D point mutation seen in our patient has not been functionally characterized, it has been reported in the context of PTEN hamartoma tumor syndrome [19].

CXCR4 mutation is a frequent event in WM (30%) and is associated with survival-independent aggressive MYD88 L265P mutated LPL [14]. However, the role of CXCR4 in the context of wild-type MYD88, such as in our patient, is unknown. CXCR4 truncation in WM has been linked with resistance to ibrutinib, but we detected CXCR4—Q318* after ibrutinib treatment [14].

B2M alterations, CD58 S212*, FOXP1 A100fs*50, POT1 N514fs*7, TNFRSF14 T169fs*65 have been reported in hematological malignancies and may be playing a pathogenic role in this case [7].

Approximately 5 years after diagnosis, we detected a novel balanced reciprocal translocation, t(10;13)(p13;q22) of uncertain significance. This translocation could represent novel gene fusions that may disrupt/dysregulate critical genes at the break points, or represent a chemotherapeutic induced passenger mutation. Interestingly, the closest reported translocation, t(10;13)(q21;q14) involving CDK1 and DGKH, is believed to be pathogenic in acute lymphoblastic leukemia/lymphoblastic lymphoma [20–23]. The new translocation we found, was detected in unstimulated cultures, which suggests a secondary myeloid related change, or less likely, a transient post-treatment hit without significant clinical impact.

4. Conclusions

The development of cancer therapeutics targeting patient-specific mutational profiles remains an active area of research. We presented a unique case of synchronous WM and LPL with novel mutations in common driver genes [24] and a unique translocation, which may inform the pathogenesis or therapeutic strategies for complex cases in the future.

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8. Duan, S.; Cermak, L.; Pagan, J.K.; Rossi, M.; Martinengo, C.; di Celle, P.F.; Chapuy, B.; Shipp, M.; Chiarle, R.; Pagano, M. FBXO11 targets BCL6 for degradation and is inactivated in diffuse large B-cell lymphomas. *Nature* **2012**, *481*, 90–93. [CrossRef]

9. Kanasugi, J.; Hanamura, I.; Ota, A.; Karnan, S.; Lam, V.Q.; Mizuno, S.; Wahiduzzaman, M.; Rahman, M.L.; Hyodo, T.; Konishi, H.; et al. Biallelic loss of FAM46C triggers tumor growth with concomitant activation of Akt signaling in multiple myeloma cells. *Cancer Sci.* **2020**, *111*, 1663–1675. [CrossRef]

10. Kyle, R.A.; Benson, J.T.; Larson, D.R.; Therneau, T.M.; Dispenzieri, A.; Kumar, S.; Melton, L.J.; Rajkumar, S.V. Progression in smoldering Waldenstrom macroglobulinemia: Long-term results. *Blood* **2012**, *119*, 4462–4466. [CrossRef]

11. McMaster, M.L. Familial Waldenstrom’s macroglobulinemia. *Semin. Oncol.* **2003**, *30*, 146–152. [CrossRef] [PubMed]

12. Ogata, K.; Kishikawa, Y.; Satoh, C.; Tamura, H.; Dan, K.; Hayashi, A. Diagnostic application of flow cytometric characteristics of CD34+ cells in low-grade myelodysplastic syndromes. *Blood* **2006**, *108*, 1037–1044. [CrossRef] [PubMed]

13. Paiva, B.; Montes, M.C.; Garcia-Sanz, R.; Ocio, E.M.; Alonso, J.; de Las Heras, N.; Escalante, F.; Cuello, R.; de Coca, A.G.; Galende, J.; et al. Multiparameter flow cytometry for the identification of the Waldenstrom’s clone in IgM-MGUS and Waldenstrom’s Macroglobulinemia: New criteria for differential diagnosis and risk stratification. *Leukemia* **2014**, *28*, 166–173. [CrossRef] [PubMed]

14. Swerdlow, S.H.; World Health Organization; International Agency for Research on Cancer. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th ed.; International Agency for Research on Cancer: Lyon, France, 2017.

15. Treon, S.P.; Hunter, Z.R.; Aggarwal, A.; Ewen, E.P.; Masota, S.; Lee, C.; Santos, D.D.; Hatjiharissi, E.; Xu, L.; Leleu, X.; et al. Characterization of familial Waldenstrom’s macroglobulinemia. *Ann. Oncol.* **2006**, *17*, 488–494. [CrossRef] [PubMed]

16. Gertz, M.A.; Anagnostopoulos, A.; Branagan, A.R.; Coleman, M.; Frankel, S.R.; Giralt, S.; Levine, T.; Munshi, N.; Pestronk, A.; et al. Treatment recommendations in Waldenstrom’s macroglobulinemia: Consensus panel recommendations from the Second International Workshop on Waldenstrom’s Macroglobulinemia. *Semin. Oncol.* **2003**, *30*, 121–126. [CrossRef] [PubMed]

17. Wang, X.; Huang, H.; Young, K.H. The PTEN tumor suppressor gene and its role in lymphoma pathogenesis. *Aging* **2015**, *7*, 1032–1049. [CrossRef] [PubMed]

18. Wang, X.; Cao, X.; Sun, R.; Tang, C.; Tzankov, A.; Zhang, J.; Manyam, G.C.; Xiao, M.; Miao, Y.; Jabbar, K.; et al. Clinical Significance of PTEN Deletion, Mutation, and Loss of PTEN Expression in De Novo Diffuse Large B-Cell Lymphoma. *Neoplasia* **2018**, *20*, 574–593. [CrossRef] [PubMed]

19. Post, K.L.; Belmadani, M.; Ganguly, P.; Meili, F.; Dingwall, R.; McDiarmid, T.A.; Meyers, W.M.; Herrington, C.; Young, B.P.; Callaghan, D.B.; et al. Multi-model functionalization of disease-associated PTEN missense mutations identifies multiple molecular mechanisms underlying protein dysfunction. *Nat. Commun.* **2020**, *11*, 2073. [CrossRef]

20. Liu, Y.F.; Wang, B.Y.; Zhang, W.N.; Huang, J.Y.; Li, B.S.; Zhang, M.; Jiang, L.; Li, J.-F.; Wang, M.J.; Dai, Y.-J.; et al. Genomic Profiling of Adult and Pediatric B-cell Acute Lymphoblastic Leukemia. *EBioMedicine* **2016**, *8*, 173–183. [CrossRef]

21. Liu, Y.; Hermanson, M.; Grander, D.; Merup, M.; Wu, X.; Heyman, M.; Rasool, O.; Jueliuson, G.; Gahrton, G.; Detlofsson, R.; et al. 13q Deletions in Lymphoid Malignancies. *Blood* **1995**, *86*, 1911–1915. [CrossRef]

22. Coignet, L.J.; Lima, C.S.; Min, T.; Streubel, B.; Swansbury, J.; Telford, N.; Swanton, S.; Bowen, A.; Nagai, M.; Catovsky, D.; et al. Myeloid- and lymphoid-specific breakpoint cluster regions in chromosome band 13q14 in acute leukemia. *Genes Chromosomes Cancer* **1999**, *25*, 222–229. [CrossRef]

23. Joy, H.P. Chromosomal and genetic abnormalities in myeloma. *Clin. Lab. Haematol.* **2002**, *24*, 259–269. [CrossRef] [PubMed]

24. Bailey, M.H.; Tokheim, C.; Porta-Pardo, E.; Sengupta, S.; Bertrand, D.; Weersinghe, A.; Colaprico, A.; Wendl, M.C.; Kim, J.; Reardon, B.; et al. Comprehensive Characterization of Cancer Driver Genes and Mutations. *Cell* **2018**, *173*, 371–385.e18. [CrossRef] [PubMed]