

Patient: Jane A. Doe



Case No: P11-00352

DOB/Gender: xx/xx/xxxx (66 yrs.) - Female  
SSN: xxx-xx-xxxx  
MRN/ID: 123456

4 Science Park, New Haven, CT 06511  
Phone: 203-787-7888 Fax: 203-823-4882  
www.precipiodx.com

Collected: xx/xx/xx  
Received: xx/xx/xx  
Reported: xx/xx/xx

Provider: John Doe, MD  
Account: Hematology Oncology Assoc  
Phone: 800-123-4567 Fax: 800-123-4444  
Copy: Joe Smith, MD

Alert Status: Routine  
Report Status: Final  
Report Category: Neoplastic

**Clinical information:** ICD-9: 273.10. Monoclonal paraproteinemia.  
Received CBC, reported on 3/6/2016: WBC 12.4; RBC 4.86; HGB 14.7; HCT 45.1; MCV 92.9; MCH 30.2; MCHC 32.6; RDW 14.1; PLT 191; MPV 8.2; LYM 54.7%; MON 'NP'; NEU 'NP'; EOS 'NP'; BAS 'NP' (NP = not provided)

**Specimens received:** 2 Formalin containers, 10 smears, 2 green-top tubes, 1 lavender-top tube

**COMPREHENSIVE DIAGNOSIS**

Professional Services Provided By  
**Yale SCHOOL OF MEDICINE**

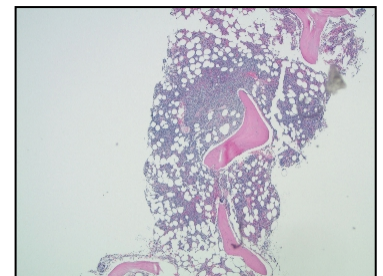
**FINAL DIAGNOSIS:**  
**Lymphoplasmacytic lymphoma (see comment)**

**COMMENT:**  
The overall findings are consistent with involvement by a LOW GRADE NON-HODGKIN B-CELL LYMPHOMA. Although the plasma cell component is morphologically limited and a clonal population of plasma cells was not definitively detected by flow cytometry or immunohistochemistry, in the setting of a monoclonal IgM of approximately 2 g/dL, the presence of a MYD88 mutation is most consistent with involvement by a LYMPHOPLASMACYTIC LYMPHOMA. Correlation with clinical and laboratory findings is advised.

Electronically signed by: S. David Hudnall, MD, FCAP

**COMPONENT DIAGNOSES**

- Biopsy: **Non-Hodgkin B-cell lymphoma (see comment)**
- Aspirate: Maturing trilineage hematopoiesis with frequent small lymphocytes
- Flow Cytometry: Suspicious for a non-Hodgkin B-cell lymphoproliferative disorder (see comment)
- Karyotyping: Normal female karyotype
- FISH: No Clonal Abnormalities Detected with probes specific for recurrent abnormalities in Plasma Cell Myeloma (see interpretation for probes tested)
- Molecular: **MYD88 mutation(s) detected: P.L265P (see comment)**



**Lymphoid Infiltrate**

**DIAGNOSIS:**

**Bone marrow, core & clot biopsies: non-Hodgkin B-cell lymphoma (see comment)**

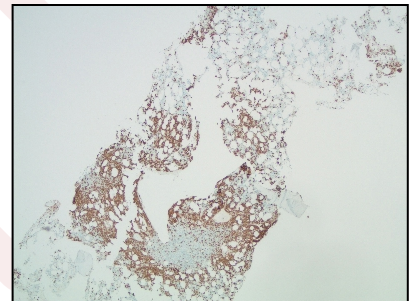
**COMMENT:**

The findings are consistent with involvement by a NON-HODGKIN B-CELL LYMPHOMA with a differential that includes a marginal zone lymphoma and lymphoplasmacytic lymphoma. Correlation with clinical and laboratory findings is advised.

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**MICROSCOPIC DESCRIPTION:**

Marrow Cellularity: Mildly hypercellular (60%)  
 Infiltrate: Approximately 30% of the cellularity is comprised of an interstitial infiltrate of lymphocytes that are small sized with round nuclei, condensed chromatin, indistinct nucleoli and small amounts of cytoplasm occurring singly and in one large aggregate.  
 Myeloid Maturation: Normal  
 Erythroid Maturation: Normal  
 Myeloid/Erythroid Ratio: Mildly increased  
 Megakaryocytes: Normal in number and morphology  
 Granulomas: Not identified  
 Iron Stain: No stainable iron is seen in this decalcified specimen  
 Marrow Reticulin: Mild increase in fibrosis is noted in association with the lymphoid aggregate  
 Marrow Trabeculae: Normal  
 Clot preparation: Similar findings to the core biopsy  
 PAS / Giemsa: Examined  
 Special Stains: Giemsa, Iron, PAS, Reticulin  
 Immunostains: CD20, CD79a and Pax-5 highlight numerous lymphocytes. An aggregate of CD3 positive T cells is seen. CD138 positive plasma cells account for less than 5% of the marrow cellularity and are polyclonal for immunoglobulin kappa and lambda light chains.



CD79a

**ADDITIONAL STUDIES:**

Stain	Result
CD3 (MRQ-39)	See microscopic description
CD20 (L26)	See microscopic description
CD79a (SP18)	See microscopic description
CD138/syndecan-1 (B-A38)	See microscopic description
Kappa (L1C1)	See microscopic description
Lambda (Lamb14)	See microscopic description
PAX5 (SP34)	See microscopic description

**GROSS DESCRIPTION:**

- The specimen is received in formalin labeled with the patient's initials and requisition number, and consists of 1 piece of bone marrow core measuring 1.0 x 0.2 x 0.2 cm. The specimen is submitted in 1 cassette after decalcification.
- The specimen is received in formalin labeled with patient's initials and requisition number, and consists of 1 piece of bone marrow clot measuring 0.5 x 1.4 x 1.4 cm. The specimen is submitted in 1 cassette.

Disclaimer: The adequacy of staining is verified by the appropriate positive and negative controls. The reagents used for these assays are analyte specific reagents (ASR). Their performance characteristics have been validated by Precipio Diagnostics, LLC, New Haven, CT. They have not been reviewed by the FDA. The FDA has deemed that such approval is unwarranted. These assays are for clinical use and should not be viewed as experimental or "research use only".

**DIAGNOSIS:**

Bone marrow, aspirate: Maturing trilineage hematopoiesis with frequent small lymphocytes

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**SMEAR REVIEW:**

The marrow aspirate smear is spicular and cellular with maturing trilineage hematopoiesis and scattered small lymphocytes. Megakaryocytes are normal in number and morphology. The myeloid : erythroid (M:E) ratio is approximately 8:1. Erythroid maturation is normal. Myeloid maturation is normal. No increase in immature cells is noted. Scant, focal iron is seen without ring sideroblasts on iron stain of the marrow aspirate.

**Number of cells counted:** 222

Cell Type	Percent	Ref. Range
Blasts	0 %	0.3 - 3.0 %
Immature Myeloid	9 %	12.0 - 21.0 %
Mature Myeloid	63 %	35.0 - 55.0 %
Eosinophils	3 %	1.0 - 3.0 %
Basophils	0 %	0.0 - 1.0 %
Lymphocytes	16 %	10.0 - 15.0 %
Plasma Cells	1 %	0.0 - 1.0 %
Monocytes	0 %	0.0 - 1.0 %
Erythroid	8 %	15.0 - 25.0 %
<b>M:E ratio</b>	<b>8:1</b>	<b>2 - 4:1</b>

**DIAGNOSIS:**

Bone marrow, aspirate: Suspicious for a non-Hodgkin B-cell lymphoproliferative disorder (see comment)

**COMMENT:**

The differential diagnosis includes lymphoplasmacytic lymphoma and a marginal zone lymphoma. Most cases of chronic lymphocytic lymphoma, mantle cell lymphoma and follicular lymphoma will express either CD5 or CD10. Correlation with the concurrent bone marrow core and aspirate morphology and cytogenetic findings is advised.

Electronically Signed By: S. David Hudnall, MD, FCAP

**INTERPRETATION:**

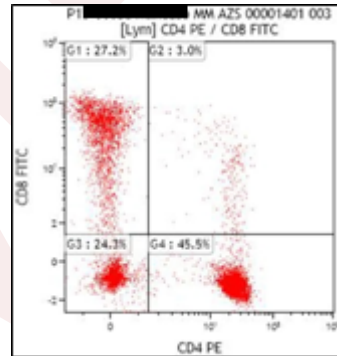
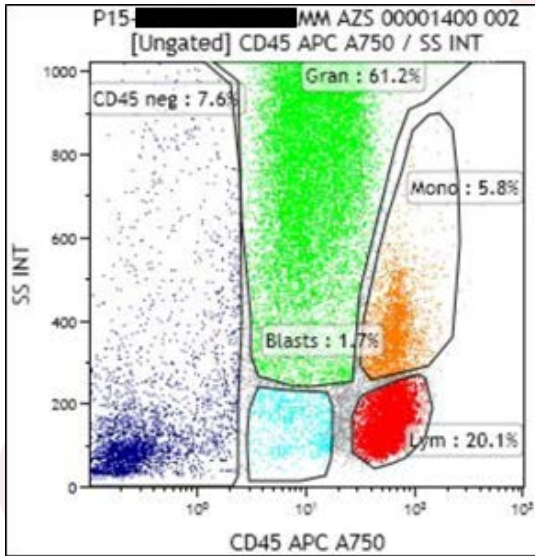
The lymphocytes (20%) include 17% B-cells with an excess of immunoglobulin kappa to lambda light chains (5:1), but are negative for CD5 and CD10. Seventy-four percent (74%) of the lymphocytes are mature T-cells with a normal CD4/CD8 ratio, and 10% natural killer (NK) cells. Less than 1% of the cellularity are plasma cells. Although excess cytoplasmic kappa light chain is detected, no cohesive population of cells is observed.

**RESULT:**

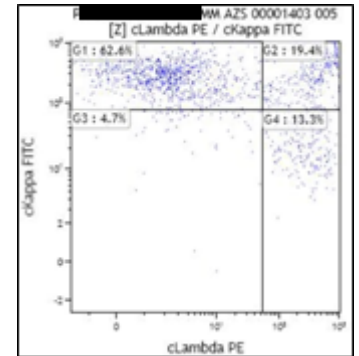
Analysis Time: xx/xx/xx 15:36

Viability: 98% (Normal > 80%)

Specimen: BM, Lavender-top tube



Normal CD4/CD8 Ratio



Kappa/Lambda B-Lymphocytes

**Flow Cytometry Differential**

Lymphocytes:	20%
Monocytes:	6%
Granulocytes:	61%
Plasma Cells:	<1%
Blasts:	2%
nRBC & Debris:	8%

**Lymphocytes Gated Population (CD45 and side scatter)**

T/NK-cell	%	B-Cell	%	Other	%
CD8	25	Kappa	13	CD45	100
CD4	48	Lambda	6		
CD56	10	CD20	17		
CD3	74	CD38	13		
CD2	82	CD10	2		
CD5	68	CD19	17		
CD7	81				

**Plasma Cells Gated Population (CD45 and side scatter)**

T/NK-cell	%	Plasma Cells	%
CD56 (Plasma Cells)	17	IgA	19
		IgG	47
		IgM	87
		cKappa	54
		cLambda	4
		CD19 (Plasma Cells)	93

Intensity: B = bright D = dim M = moderate

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**DIAGNOSIS:**

Bone marrow, aspirate: Normal female karyotype

Electronically signed by: S. David Hudnall, MD, FCAP

**INDICATION:**

Monoclonal paraproteinemia

**KARYOTYPE "ISCN":**

46,XX[20]; Normal Female Karyotype

**INTERPRETATION:**

Conventional cytogenetic analysis shows a female karyotype with no evidence of an acquired clonal abnormality. This does not exclude the possibility of an abnormality that cannot be detected at the chromosomal level or exists at a low residual level.

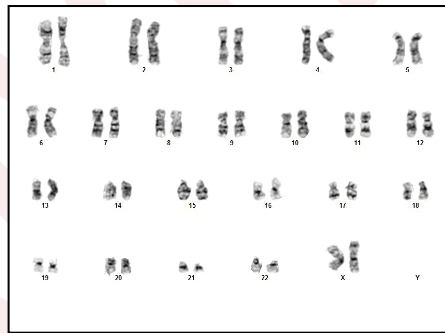
Interpretation of this specimen's cytogenetic results should be made in conjunction with morphologic, immunophenotypic, and clinical findings. The results of this analysis do not exclude the possibility of genetic alterations below the band-resolution of this test or abnormalities due to other etiologies.

FISH studies are recommended and much more sensitive than G-band analysis for cases of plasma cell neoplasia because plasma cells have a very low proliferation rate in culture. FISH studies are recommended for clinically-significant abnormalities. (NCCN Guidelines, ver 2.2013, Multiple Myeloma, National Comprehensive Cancer Network, nccn.org)

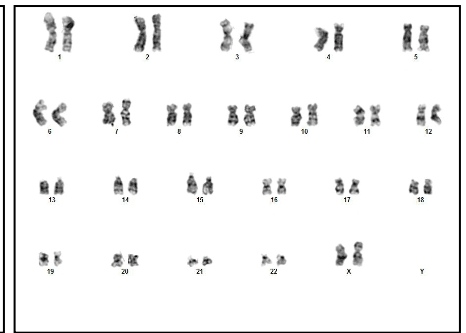
**RESULT:**

**Analysis**

Cells Counted:	20
Cells Analyzed:	20
Cells Imaged:	3
Cells Karyotyped:	3
Banding Type:	G-Banding
Band Level:	450



Normal Karyotype



Normal Karyotype



**DIAGNOSIS:**

Bone marrow, aspirate: No Clonal Abnormalities Detected with probes specific for recurrent abnormalities in Plasma Cell Myeloma (see interpretation for probes tested)

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**FISH "ISCN":**

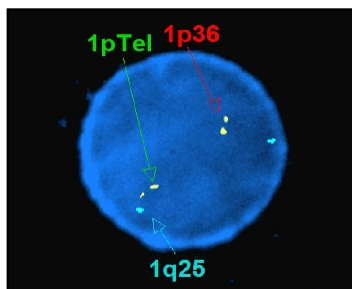
nuc ish (p58x2,1q25x2)[200],[CEP9x2][200],[CCND1x2,IGHx2][200],[D13S319x2,13q34x2][200],[p53x2][200]

**INTERPRETATION:**

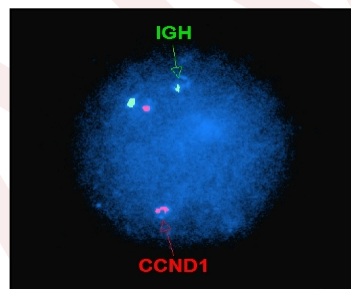
Fluorescence in situ hybridization (FISH) with a panel of probes specific for detection of recurring chromosome abnormalities in plasma dysplasia was performed on uncultured bone marrow cells.

The regions/loci represented in these probe mixes were:

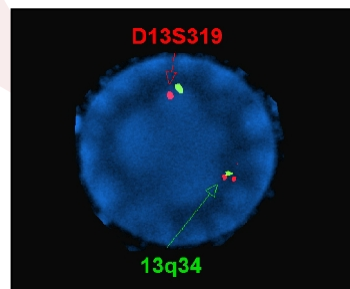
1. IGH/CCND1 dual color, dual translocation probes to 11q13 & 14q32 regions respectively, reveal a hybridization pattern within normal limits in 200 analyzed nuclei.
2. P53 (17p13.1), used to detect deletion/copy number abnormalities of chromosome 17p, reveals a hybridization pattern within normal limits in 200 analyzed nuclei.
3. 1p36 Microdeletion Region Probe - LSI p58 (1p36)/TelVysion 1p/LSI 1q25, used to detect copy number abnormalities of chromosome 1, reveal a hybridization pattern within normal limits in 200 analyzed nuclei.
4. CEP9 (centromere probe to chromosome 9), used to detect copy number abnormalities of chromosome 9, reveals a hybridization pattern within normal limits in 200 analyzed nuclei.
5. D13S319 (13q14.3) and 13q34, used to detect copy number abnormalities/deletion of chromosome 13, reveal a hybridization pattern within normal limits in 200 analyzed nuclei.



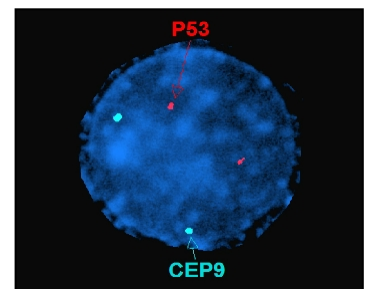
Normal Chromosome 1



No IGH/CCND1 Translocation



No 13q14.3 Deletion



No P53 Deletion/Trisomy 9

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**DIAGNOSIS:**

Bone marrow, aspirate: MYD88 mutation(S) detected: P.L265P (see comment)

Electronically Signed By: S. David Hudnall, MD, FCAP

**INTERPRETATION:**

MYD88 mutation is the most frequent genomic abnormality in diffuse large cell lymphoma (DLBCL) activated B-cell-like (ABC) subtype, detected in 40% of cases. MYD88 is rarely mutated in the germinal center B-cell-like (GCB) DLBL, therefore, it can be used to differentiate between the two subtypes. MYD88 mutation is detected in approximately 90% of cases of Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma. MYD88 mutation analysis can be a useful prognostic tool for patients with IgM-MGUS since the L265P mutation is associated with a higher risk of disease progression and a greater disease burden. MYD88 mutation has also been reported to be common (40%) in central nervous system lymphoma.

**METHODOLOGY:**

Total nucleic acid was extracted from patient's plasma, PB/BM cells or paraffin-embedded tissues (FFPE). Bi-directional Sanger sequencing of exon 5 of MYD88 was performed, including the L265P mutation hot spot. This is a sequencing-based assay which has a typical sensitivity of 10-15% for detecting MYD88 mutations in a wild-type background. Various factors including quantity and quality of nucleic acid, sample preparation, and sample age can affect assay performance.

**REFERENCES:**

1. Trøen G, Warsame A, Delabie J. CD79B and MYD88 Mutations in Splenic Marginal Zone Lymphoma. *ISRN Oncol.* 2013;2013:252318.
2. Xu L, et al. MYD88 L265P in Waldenstrom's macroglobulinemia, IgM monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific PCR. *Blood.* 2013;121(11):2051-2058.

The performance characteristics of this test have been determined by the laboratory. This test has not been approved by the FDA. The FDA has determined such clearance or approval is not necessary. The laboratory is CLIA certified to perform high complexity clinical testing.