Plasma cell neoplasms and lymphoplasmacytic lymphoma

Valentina Nardi, MD

Associate Pathologist,
Massachusetts General Hospital,
Associate Professor of Pathology,
Harvard Medical School

Tour De Force B
David Gerstein
(2018)

There are no disclosures for this speaker

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Plasma cell neoplasms

Table 13.04 Plasma cell neoplasms

Non-IgM (plasma cell) monoclonal gammopathy of undetermined significance (precursor lesion)	Clinical variants
Plasma cell myeloma	Smouldering (asymptomatic) plasma cell myeloma Non-secretory myeloma Plasma cell leukaemia
Plasmacytoma	Solitary plasmacytoma of bone Extraosseous (extramedullary) plasmacytoma
Monoclonal immunoglobulin deposition diseases	Primary amyloidosis Systemic light and heavy chain deposition diseases
Plasma cell neoplasms with associated paraneoplastic syndrome	POEMS syndrome TEMPI syndrome (provisional)

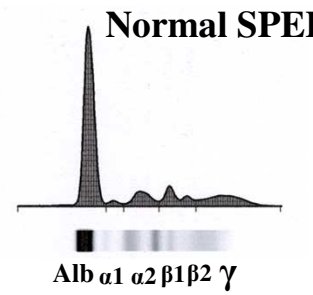
(WHO Classification of tumors of hematopoietic and lymphoid tissues, Revised 4th edition, 2016)

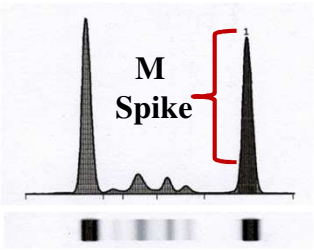
Diagnostic criteria for PCM, SMM, MGUS

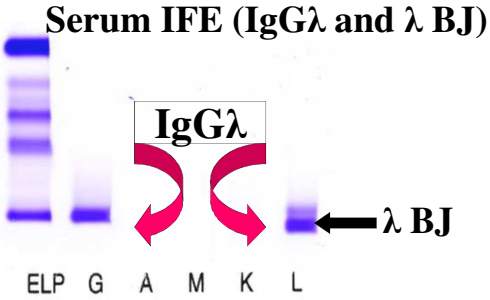
		MGUS	SMM	MM	
				Biomarker	CRAB
	M-Protein < 30 g/l	→			
	BM PC < 10%	→			
	M-Protein > 30 g/l		→		
	BM PC > 10%		→		
	BM PC > 60%			→	
	FLC ratio > 100			→	
	MRI ≥ 2 focal lesions			→	
C	Hypercalcemia				→
R	Renal failure				→
A	Anemia				→
B	Bone disease				→

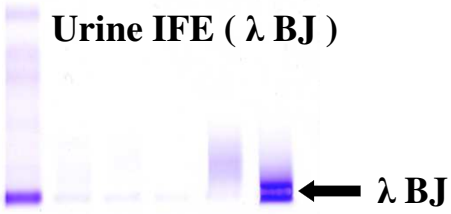
(Caers J., et al, Haematologica 2018)

Ancillary studies: Protein Electrophoresis (SPEP/UPEP) and Immunofixation to identify the M component



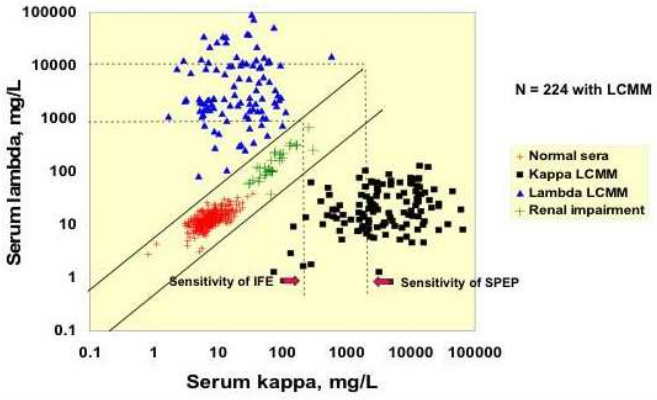






Ancillary studies: Serum Free Light chain assay (FLCs)

- Useful for detection and monitoring of light chain MM (LCMM), oligosecretory MM, but also for ~95% of secretory MM
- Increased sensitivity over SPEP and IFE allowing earlier assessment of changes in tumour mass (FLC half life: 2-4h; IgG half-life: 20–25 days)



Adapted from A. Bradwell et al, Lancet 2003

Nonsecretory (NS) and Light Chain (LC) Escape in Patients With Multiple Myeloma

2%- 4% myeloma

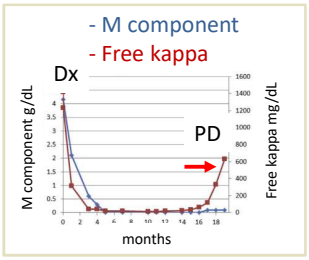
1) lose the ability to produce the paraprotein →"nonsecretory escape"

2) switch the production from intact immunoglobulin to light chain (LC) only →"LC escape"

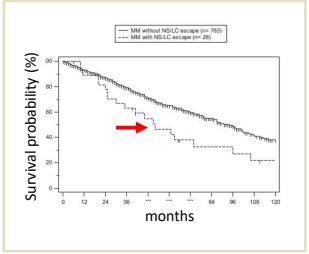
Table 1 Patient Characteristics in Multiple Myeloma With NS and LC Escape and Without NS/LC Escape

	NS Escape (N = 13)	LC Escape (N = 15)	Without NS/LC Escape (N = 763)	P
Median age, y (range)	65 (53-80)	64 (37-75)	65 (23-94)	.80
Male gender	9 (69)	8 (53)	447 (59)	.82
Paraprotein isotype				.21
IgG-kappa	5	8	282 (37)	
IgG-lambda	3	3	138 (18)	
IgA-kappa	2	0	91 (12)	
IgA-lambda	1	4	60 (8)	
Kappa LC	1	Not applicable	99 (13)	
Lambda LC	1	Not applicable	62 (8)	
Other	0	0	31 (4)	
Median calcium, g/dL (SD)	10.7 (±1.0)	10.7 (±1.8)	9.5 (±1.7)	.12
Median creatinine, mg/dL (SD)	1.5 (±0.8)	1.1 (±1.0)	1.1 (±2.6)	.08
Median Hb, g/dL (SD)	9.6 (±2.3)	9.5 (±2.6)	10.7 (±2.6)	.04
Lytic lesions at skeletal survey	9/12 (75%)	6/10 (60%)	419/675 (62%)	.56
Durie-Salmon stage III	9/11 (82%)	7/11 (64%)	382/635 (60%)	.24
ISS stage III	6/8 (75%)	8/12 (67%)	206/607 (34%)	< .01
Abnormal metaphase cytogenetics (except deletion Y)	2/10 (20%)	2/8 (25%)	85/586 (14%)	.36
High-risk FISH*	5/12 (42%)	4/8 (50%)	101/576 (18%)	< .01
Relapse/progression with EMD	5 (38%)	3 (20%)	58 (8%)	< .01

LC escape at disease progression



OS with or without NS/LC escape

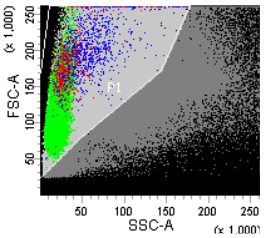


Patel U.H. et al. Clinical Lymphoma, Myeloma & Leukemia (2018)

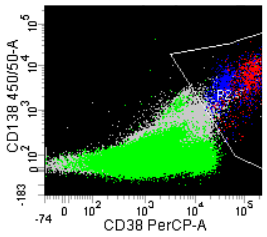
Ancillary studies: Flow cytometric analysis of plasma cells

- Cyto-chex BCT tubes for specimen collection can help preserve viability of plasma cells
- Gating by FSC, SSC, CD45, CD38, CD138. Looking for aberrant expression of CD56 (+),CD27 (-) CD19 (-) and light chain restriction

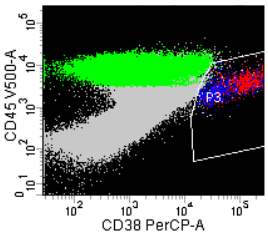
Size (FSC) & complexity (SSC)



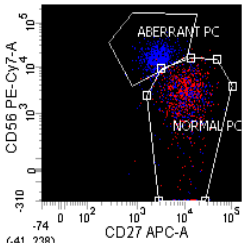
CD38 bright &CD138 bright



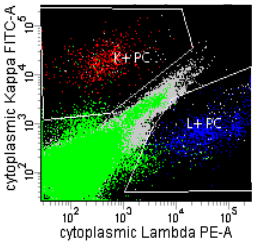
CD38 bright &CD45 dim



CD56 Pos & CD27 dim to neg

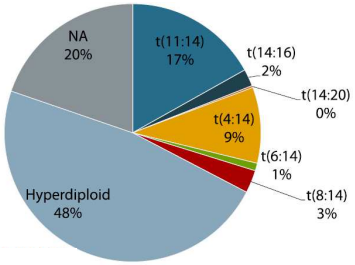


Light chain restriction (lambda here)



Other:
CD117+ (? Good pgn)
CD20+ (t(11;14))
CD28 (treatment failure)
CD81+ (poor pgn?)
CD200+

Recurrent genetic abnormalities and prognosis

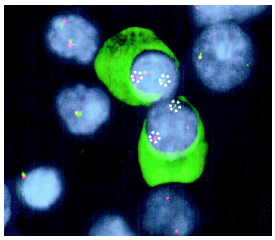


- ***Conventional cytogenetic (karyotype)*** *detects aberrations in just ~30% of cases*
- ***FISH*** *should detect cytogenetic aberrations in >90% of cases*

Abnormality	Gene(s)/Region(s)	Prognostic Significance	Other Information
Aneuploidy			
- Hyperdiploid	N/A	Favorable	Common trisomies: 3, 5, 7, 9, 11, 15, 19, 21
- Near-tetraploid	N/A	Unfavorable	
Monosomy 13	Predominantly 13q14	Unfavorable	85% monosomy, 15% deletion
IGH Translocations			Uncommonly *IGL* (immunoglobulin light chain) translocations
- t(4;14)(p16.3;q32)	*FGFR3/MMSET*	Unfavorable	
- t(11;14)(q13;q32)	*CCND1*	Favorable / Neutral	
- t(14;16)(q32;q23)	c-*maf*	Unfavorable	
- other *IGH* translocations	*CCND3*, *mafB*, *MUM1*, etc.	Unknown	
c-*myc* translocations		Unfavorable	Decreased OS and PFS
TP53 biallelic inactivation	17p13	Unfavorable	Decreased OS and PFS

Ancillary studies : IF-FISH or FISH on flow/bead sorted abnormal plasma cells for detecting recurrent genetic abnormalities

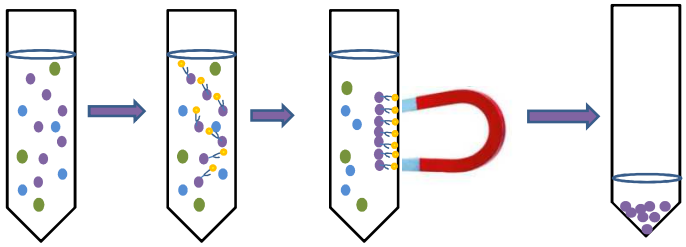
IF FISH



Example of IgH rearrangement (t(14q32)) by double-color FISH & cytoplasmic Ig-light-chain staining (using an IgH break-apart probe)

(Boersma-Vreugdenhil G.A., et al., Blood 2003)

Magnetic Bead sorting of plasma cells



Plasma cells Anti CD138 conjugated to magnetic bead

Ancillary studies: IF-FISH or FISH on flow/bead sorted abnormal plasma cells for detecting recurrent genetic abnormalities

FISH panels for PCN

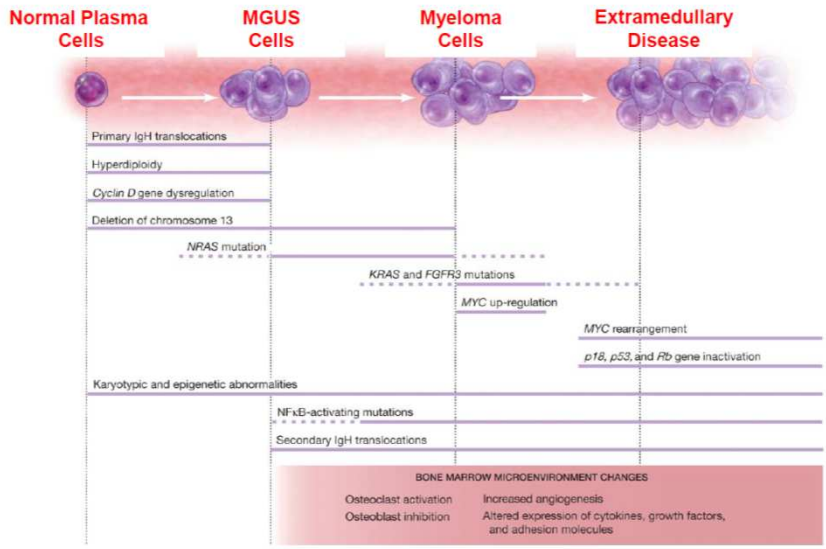
The initial panel for plasmacytoma specimens includes testing for the following abnormalities using the probes listed:
17p-, *TP53*/D17Z1
1q gain, *TP73*/1q22
8q24.1 rearrangement, *MYC*
-13/13q-, *RB1*/*LAMP1*
+9/+15, D9Z1/D15Z4
+3/+7, D3Z1/D7Z1
14q32 rearrangement, *IGH*
t(11;14)(q13;q32), *CCND1*/*IGH*

The initial panel for sorted BM plasma cells Includes:
17p-, TP53/D17Z1
1q gain, TP73/1q22
14q32 rearrangement, IGH break-apart

Based on the results from the initial panel, reflex testing may be performed to identify the following abnormalities using the probes listed:
t(11;14)(q13;q32), CCND1/IGH fusion
t(14;16)(q32;q23), IGH/MAF fusion
t(4;14)(p16.3;q32), FGFR3/IGH fusion
t(14;20)(q32;q12), IGH/MAFB fusion

For f-up specimens:
17p-, TP53/D17Z1
1q gain, TP73/1q22
8q24.1 rearrangement, MYC break-apart

Evolution of multiple myeloma- Genetic changes

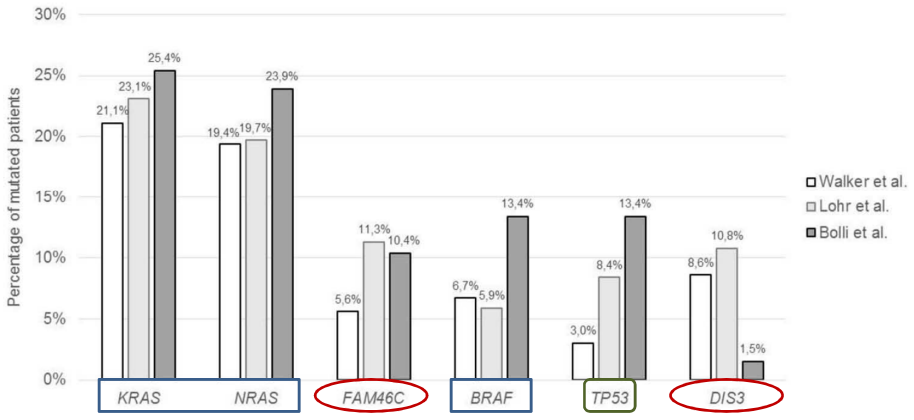


Neha Korde et al. Blood 2011;117:5573-5581

blood

Ancillary studies : NGS, for prognosis and to inform therapy

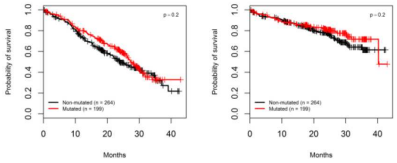
- Gene mutations are thought to be secondary events associated with tumor progression rather than initiation
- Only a few genes are mutated at a significant frequency (>5%) in multiple cohorts



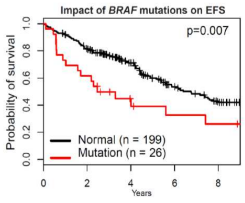
Lionetti M. and Neri A., Expert review of molecular diagnostics 2017

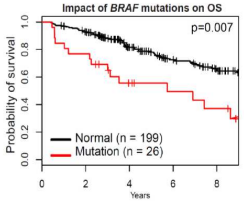
Ancillary studies : NGS, for prognosis and to inform therapy

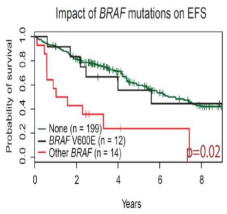
KRAS and NRAS mutations: no prognostic value with current treatments

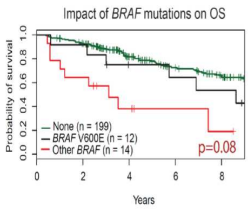


BRAF mutations: adverse EFS and OS, particularly non V600E mutations









Walker JCO 2015

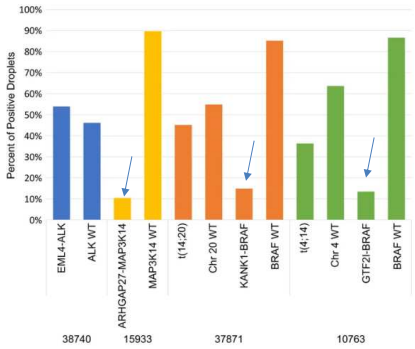
Ancillary studies : NGS to detect actionable fusion detection

- ~1.5% MM have gene fusions, many activating kinases (actionable)

Head gene	Head last exon	Tail gene	Tail first exon	In-frame
SND1	10	*BRAF*	11	Yes
TPR	10	*NTRK1*	3	Yes
CDC27	4	*MAP3K14*	4	Yes
FCHSD2	2	*MAP3K14*	4	Yes
NMT1	1	*MAP3K14*	4	Yes
EFTUD2	11	*MAP3K14*	3	Yes
TPM3	6	*NTRK1*	10	Yes

Head gene	Head last exon	Tail gene	Tail first exon	In-frame
CREB1	1	*ALK*	9	Yes
TAF15	3	*MAP3K14*	6	Yes
YBX1	2	*MAP3K14*	4	Yes
IKZF3	1	*MAP3K14*	4	Yes
ARHGEF2	21	*NTRK1*	12	Yes
BRAF	7	*AGK*	3	Yes

- Gene fusions can be clonal or subclonal



ddPCR with probe specific for fusion gene breakpoints, Unrearranged (WT) alleles, IGH translocation breakpoints

Morgan G., et al. Leukemia 2018

Ancillary studies : NGS to inform treatment

Table 1. Genes affected by druggable mutations in MM.

Gene	Percentage of mutated MM patients	Targeted therapy
KRAS	23.2%	MEK inhibitor
NRAS	21%	MEK inhibitor
BRAF	8.7%	Vemurafenib
ROS1	3.1%	Foretinib
CCND1	2.7%	Pablociclib
FGFR3	1.5%	Masitinib
MLL	1.2%	EPZ-5676
PIK3CA	1.2%	GDC-0941
FGFR2	1.2%	Masitinib
FLT3	1%	Sunitinib

Obstacles to success for targeted therapies:

- ❖ Clonal heterogeneity
- ❖ Most of the reported mutated genes have very low to undetectable expression

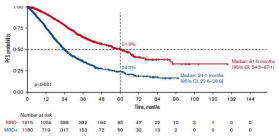
Lionetti M. and Neri A., Expert review of molecular diagnostics 2017

Measurable residual disease (MRD) in MM

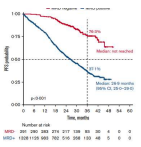
- MRD as surrogate for survival
- MRD negativity (=absence of clonal plasma cells in BM aspirates using methods with a minimum detection capability of 1 in 10^5 nucleated cells) is one of the goals of therapy

Meta-analysis: reduction in risk of progression and mortality in patients in CR who achieved MRD negativity (<10^-5)

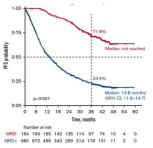
PFS Newly diagnosed -Transplant eligible



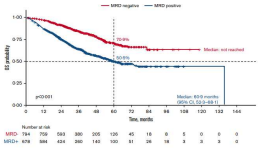
PFS Newly diagnosed -Transplant ineligible



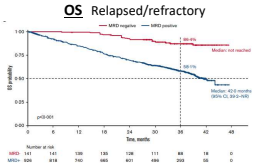
PFS Relapsed/refractory



OS Newly diagnosed -Transplant eligible



OS Relapsed/refractory

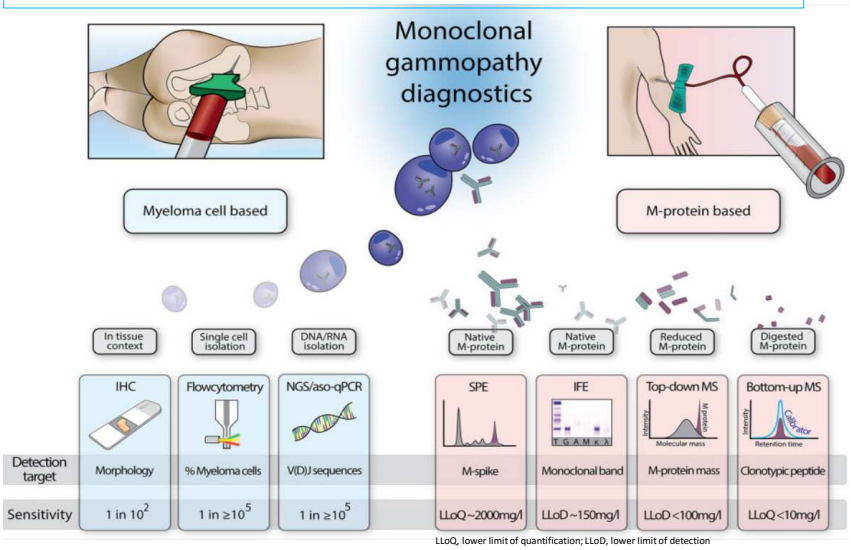


Munshi N. et al, Blood 2020
Munshi N et al, JAMA Oncol 2017

- Meta-analysis: 44 eligible studies with PFS data from 8098 patients;
- 23 studies with OS data from 4297 patients

Monitoring Of MRD in MM

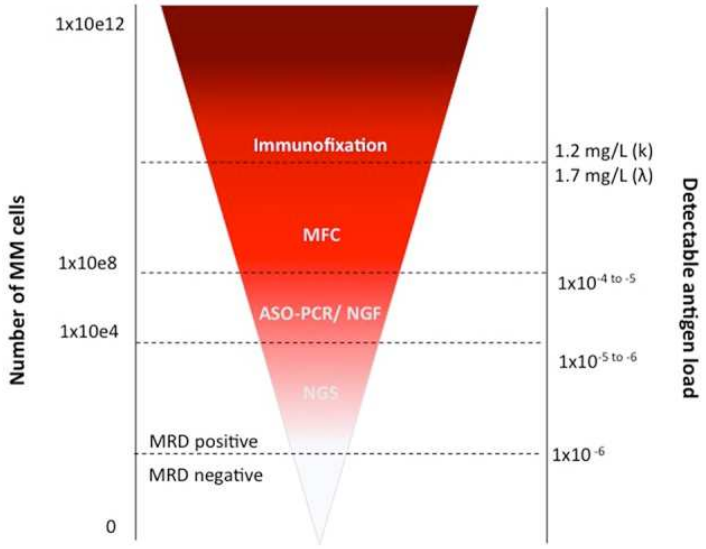
MRD negativity :
absence of clonal plasma cells in BM aspirates using methods with a minimum detection capability of 1 in 10^5 nucleated cells.



LLoQ, lower limit of quantification; LLoD, lower limit of detection

M. Zajec et al. Clinical Chemistry 66:3 421–433 (2020)

Sensitivity of MM cell-based methods for MRD detection



Romano A., et al. Front Oncol 2019

MRD by Flow cytometric analysis

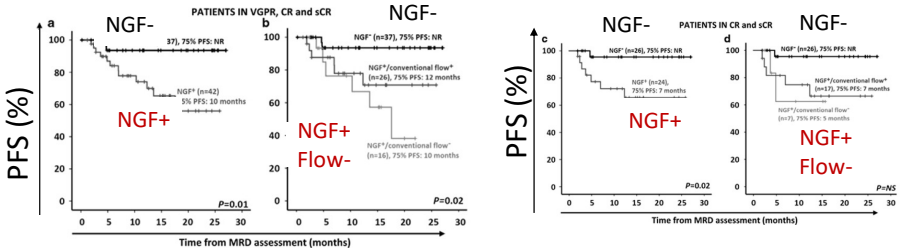
EuroFlow-based next generation flow (**NGF**) approach for MRD

- optimized combination of fluorochromes and antibody reagents, 8-color, 2 tubes assay*
- 12 different markers (CD38, CD138, CD45, CD19, CD27, CD28, CD56, CD81, CD117, Ig-kappa and Ig-lambda, and β2-microglobulin)

- Cell viability
- Spatial heterogeneity
- Hemodilution

* *Some leading groups use a 10-color 1 tube NGF with similar sensitivity*

→ LOD ~10^-5 -10^-6 vs conventional flow-MRD ($<10^{-4}$) vs ASOqPCR and NGS ($<10^{-5}$–10^{-6})



Flores-Montero J et al., Leukemia 2017

MM MRD by NGS

Commonly used is the FDA approved NGS based clonoSEQ assay identifies rearranged IgH (VDJ), IgH (DJ), IgK, and IgL receptor gene sequences, translocated BCL1/IgH (J) and BCL2/IgH (J) sequences using PCR.
LOD 10^-6

- ❑ Spatial heterogeneity & patchy nature of MM
- ❑ Bone marrow hemodilution

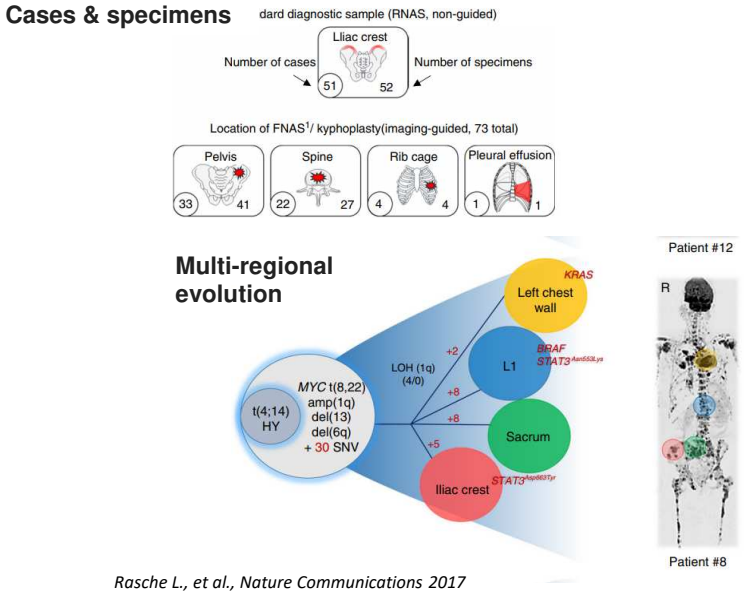
false neg BM MRD

Ongoing research on non-invasive MRD monitoring:

- ➢ Searching for circulating tumor cells (**CTCs**) by MFC
- ➢ Monitoring IG rearrangements in circulating free DNA (**cfDNA**) by NGS
- ➢ Monitoring of single nucleotide variants (SNVs) in **cfDNA**
- ➢ Immune positron emission tomography (**PET**)
- ➢ M-protein based assays

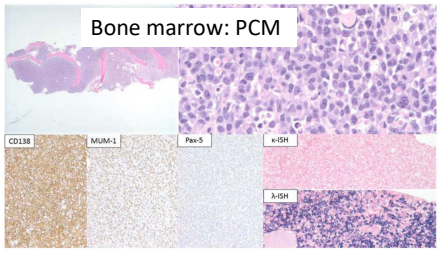
Rasche L, et al, Leukemia 2019; Waldschmidt JM et al., Semin Hematol. 2018;
Manasanch EE., Am Soc Hematol Educ Program. 2019; Biancon G., et al, JMD 2018;

Spatial genomic heterogeneity in multiple myeloma revealed by multi-region sequencing

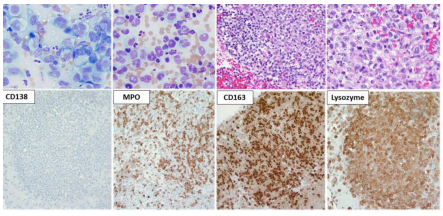


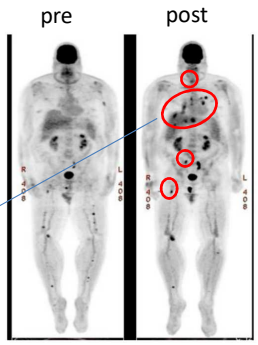
Rasche L., et al., Nature Communications 2017

Myeloid transformation of plasma cell myeloma: molecular evidence of clonal evolution revealed by next generation sequencing



Mediastinal lymph node: myeloid sarcoma





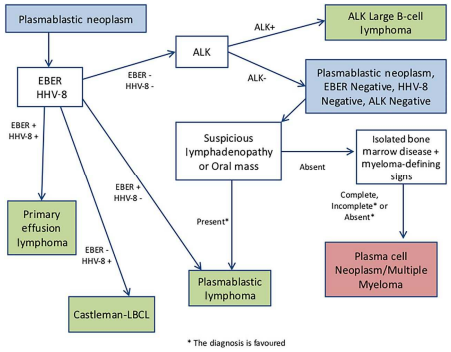
Bone marrow aspirate	Soft tissue
BRAF1 G466A subclonal, G469 subclonal	*BRAF* G469A
KRAS A146V	*KRAS* A146V
IGH IGH-MAF rearrangement	*IGH* IGH-MAF rearrangement
CDKN2A/B loss	*CDKN2A/B* loss
MAP3K6 Q943, truncation exon 22	*MAP3K6* Q943, truncation exon 22
TRAF3 R505	*NF1* R2450
PTPRO E379K – subclonal	*CCT6B* splice site 615-2A > G *TNFAIP3* W85

Gralewski et al. Diagnostic Pathology (2018)

Distinguishing between tumours with plasmablastic morphology

- **Plasmablastic lymphoma (PBL)**
- **Plasmablastic myeloma (PCM)**
- ALK+ large B-cell lymphoma (ALK/LBL)
- Large B-cell lymphoma arising in HHV-8–associated multicentric Castleman
- Primary effusion lymphoma (PEL)

Proposed diagnostic algorithm for tumours with plasmablastic morphology



Janice S Ahn et al. J Clin Pathol 2017;70:775-780

Plasmablastic lymphoma vs plasmablastic myeloma

Table 1: Differences between clinical and immunophenotypic profile of plasmablastic lymphoma, ALK+large B-cell lymphoma, and plasmablastic myeloma

Parameter	*Plasmablastic lymphoma*	*Anaplastic lymphoma kinase-positive large B-cell lymphoma*	*Plasmablastic myeloma*
Clinical features	Lymphadenopathy/ oral mass favors		Myeloma defining clinical features - hypercalcemia, anemia, renal failure, bone lesions, or isolated bone marrow disease favors
M band	Variable		Variable
CD45	Variable	Variable	Variable
CD20	–	–	–
PAX5	–	–	–
CD38	+	+	+
CD138	+	+	+
CD79a	Variable	–	–
IRF4/MUM1	+	+	+
CD56	Variable (usually –)	–	Usually +
Cytoplasmic Ig light chains	+	+	+
EMA	Variable	+	+
CD30	Variable	–	–
EBV-EBER	Variable - positivity favors PBL~60%	–	–
Association with HIV	+	–	–
Others	BLIMP1+	ALK+, BOB1, OCT2, *ALK* gene rearrangement	–

EBER: Epstein-Barr virus encoded RNA; EBV: Epstein-Barr virus; HIV: Human immunodeficiency virus; PBL: Plasmablastic lymphoma; ALK: Anaplastic lymphoma kinase; EMA: Epithelial membrane antigen; +: Often positive, -: Often negative

Sreedharanunni S et al., Indian J Pathol Microbiol 2019

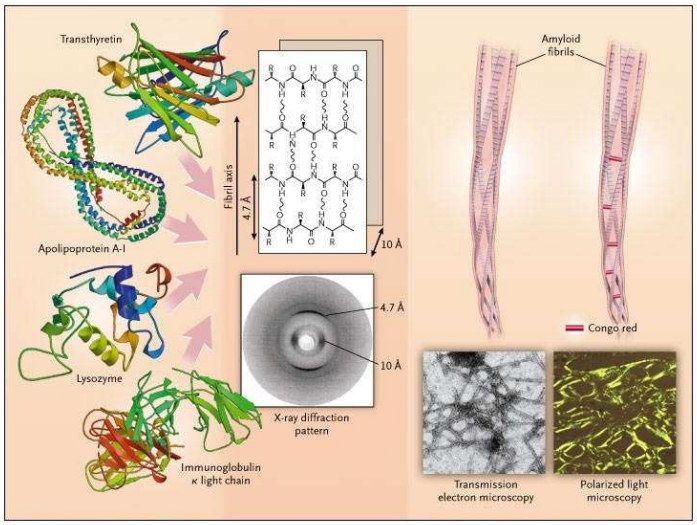
Other plasma cell neoplasms

Monoclonal immunoglobulin deposition diseases	Primary amyloidosis Systemic light and heavy chain deposition diseases

(WHO Classification of tumors of hematopoietic and lymphoid tissues, Revised 4th edition)

Amyloidosis

Heterogeneous group of disorders characterized by misfolded protein that deposits in organs compromising their structure and function



Merlini G. and Bellotti V.
N Engl J Med 2003

Amyloidosis

>30 subtypes of proteins can cause amyloidosis, but only 14 cause systemic disease

Table 1. Amyloid Proteins and Their Precursors.*

Amyloid Protein	Precursor	Distribution	Type	Syndrome or Involved Tissues
Aβ	Aβ protein precursor	Localized Localized	Acquired Hereditary	Sporadic Alzheimer's disease, aging Prototypical hereditary cerebral amyloid angiopathy, Dutch type
APrP	Prion protein	Localized Localized	Acquired Hereditary	Sporadic (iatrogenic) CJD, new variant CJD (alimentary?) Familial CJD, GSSD, FFI
ABri	ABri protein precursor	Localized or systemic?	Hereditary	British familial dementia
ACys	Cystatin C	Systemic	Hereditary	Icelandic hereditary cerebral amyloid angiopathy
Aβ2M	Beta$_2$-microglobulin	Systemic	Acquired	Chronic hemodialysis
AL	Immunoglobulin light chain	Systemic or localized	Acquired	Primary amyloidosis, myeloma-associated
AA	Serum amyloid A	Systemic	Acquired	Secondary amyloidosis, reactive to chronic infection or inflammation including hereditary periodic fever (FMF, TRAPS, HIDS, FCU, and MWS)
ATTR	Transthyretin	Systemic Systemic	Hereditary Acquired	Prototypical FAP Senile heart, vessels
AApoAI	Apolipoprotein A-I	Systemic	Hereditary	Liver, kidney, heart
AApoAII	Apolipoprotein A-II	Systemic	Hereditary	Kidney, heart
AGel	Gelsolin	Systemic	Hereditary	Finnish hereditary amyloidosis
ALys	Lysozyme	Systemic	Hereditary	Kidney, liver, spleen
AFib	Fibrinogen Aα chain	Systemic	Hereditary	Kidney

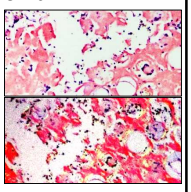
Merlini G. and Bellotti V. N Engl J Med 2003

AL Amyloidosis

- Most common type of systemic amyloidosis
- Incidence of 9–14 cases per million-person years in the USA
- Occurs in 12-15% of patients with myeloma (also lymphoplasmacytic neoplasms)
- 80% lambda , 20% kappa
- Usually presents with nonspecific symptoms (weight loss, fatigue, dyspnea, paresthesias)
- Highly specific but quite insensitive are macroglossia (10%) and periorbital purpura (<20%)
- The most commonly involved organs are the heart, kidneys, liver, nervous system, gastrointestinal tract and soft tissue

AL Amyloidosis-diagnosis

- ❑ Presence of systemic syndrome (proteinuria, heart failure with preserved ejection fraction, unexplained hepatomegaly, peripheral autonomic neuropathy, nephrotic syndrome, malabsorption) or atypical MGUS or smoldering myeloma
- ❑ Histological documentation of amyloid by Congo-red stain: Salivary gland sensitivity (89%)> fat pad (78%) > bone marrow (70%)



- ❑ Evidence of a monoclonal plasma cell disorder (in the serum, the urine or in a bone marrow biopsy).
- ❑ Systemic (not just localized i.e. to skin, urinary tract, orbit, colon) production of light chains (Serum amyloid P component scintigraphy)
- ❑ Amyloid typing:
  - -Immunohistochemistry (IHC)
  - -Immunoelectron microscopy (IEM)
  - -Mass spectrometry (gold standard)
- ❑ 40% have t(11;14) vs 15% for Myeloma or non IgM MGUS

	Immuno-histochemistry	Immunoelectron microscopy	Mass spectrometry
Accessibility	Widely available,	Not available in most centers	Not available in most centers
Sensitivity (%)	75–80	75–80	95
Specificity (%)	80	100	100
Comments	Should be done by highly specialized pathologist, non-standardized,		The gold standard for AL amyloidosis typing

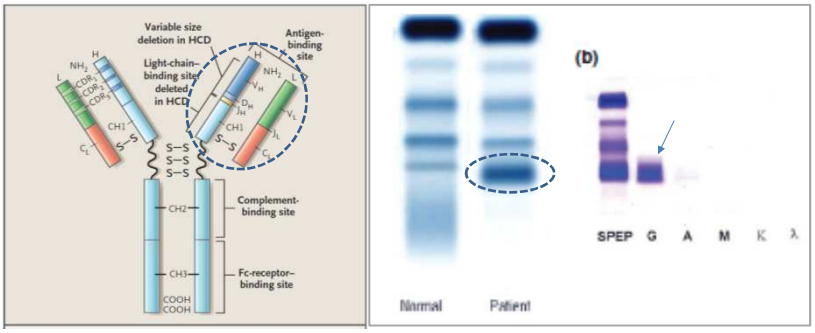
Vaxman I., Dispenzieri A., Muchtar E., and Gertz M., Blood Reviews 2019

Light chain deposition diseases (LCDD)

- ❖ Rare (~5% of myeloma at autopsy)
- ❖ Deposition of non-amyloid monoclonal light chains in multiple organs
- ❖ 80% kappa light chains
- ❖ 50-60% of patients have plasma cell myeloma while 17% have MGUS or no clonal plasma cells; can also complicate other B-cell lymphomas, such as LPL, MZL, CLL
- ❖ Although any organ can be involved kidneys are always affected
- ❖ Diagnosis: serum and protein electrophoresis with immunofixation and quantitative serum free light chain assay

Heavy chain deposition diseases

- Rare variants of B-cell lymphomas that produce one of three classes of immunoglobulin heavy chains (alpha, mu, or gamma) without a bound light chain



- Prognosis of HCDs is variable
- No standardized effective treatment programs are available but early-stage alpha-HCD may respond to antibiotics

Ho YH et al., Cytopathology 2014; Munshi NC., et al, NEJM 2008

Alpha Heavy chain disease

aka **I**mmunoproliferative **s**mall **i**ntestinal **d**isease (**IPSID**)
(although rare respiratory and lymphomatous forms have been reported)

-- Most common of the HCD

-- **MALT lymphoma** in the small intestine in young adults (20s-30s) living in conditions of poor sanitation (Mediterranean, Norther African and Middle East descent)

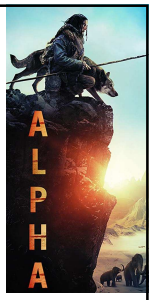
-- **Campylobacter jejuni** infection has been implicated in its pathogenesis

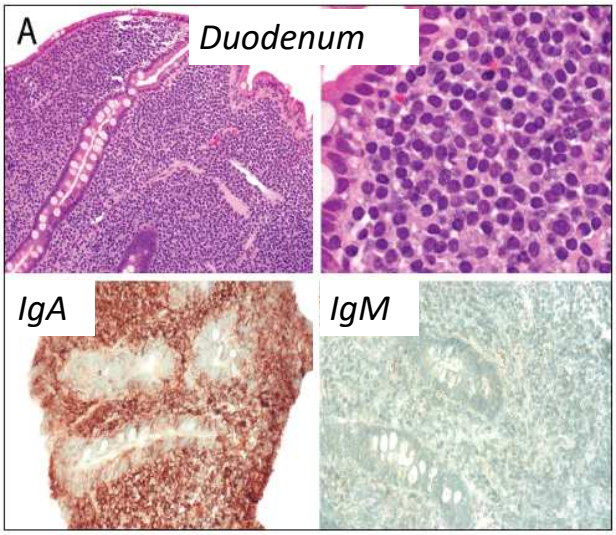
-- Abdominal pain, severe malabsorption with chronic diarrhea, steatorrhea and weight loss and occasionally mesenteric lymphadenopathy

-- 50% not a distinct band or sharp peak on electrophoresis and otherwise polymers of different sizes (broad band in alpha-2 or beta mobility regions)

-- Natural history is local progression, followed by systemic spread. Complications (bowel obstruction or perforation, severe malnutrition or infection) may be fatal. Progression to a large cell lymphoma can occur. In early disease, 6-month antimicrobial treatment leads to remission in 30-70% of cases

Alpha Heavy chain disease

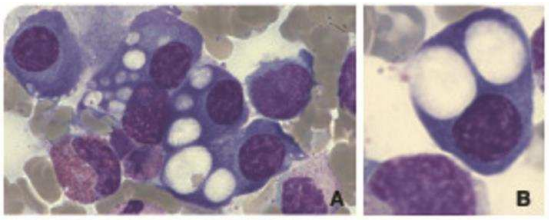




Bianchi G. et al, Oncology (Williston Park). 2014

Mu Heavy chain disease

- extremely rare disorder with a male predominance; ~ 6th decade
- clinical features resemble **CLL/SLL** (i.e. anemia, hepatosplenomegaly, lymphocytosis). The spleen is almost universally involved, with hepatic involvement in 75% of patients, nodal disease in 40%, and BM in 20% (lytic lesions)
- **Hypogammaglobulinemia** is a prominent feature
- The prognosis is highly variable with overall survival (OS) reported to range from <1 month to decades (median OS: 2 years)
- Histology: vacuolated plasma cells and small lymphoid cells



ASH image bank #61101

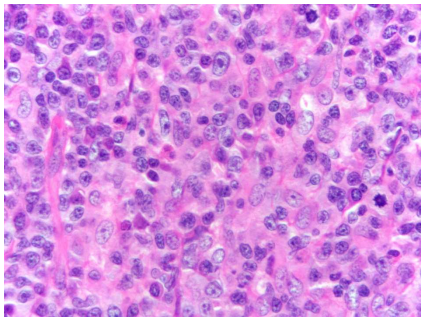
Gamma Heavy chain disease

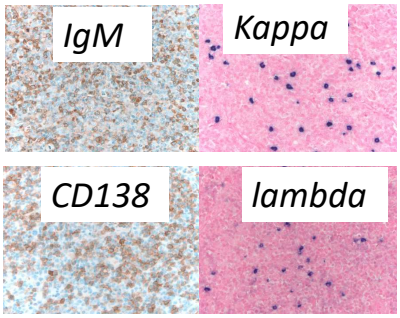
- intermediate in frequency between alpha and mu HCD, F>M, age 50s-70s
- typically **associated with a systemic lymphoma** (LPL)
- Heterogeneous presentation (from asymptomatic to very sick) and a highly variable clinical course with overall survival ranging from <1-20 years.
- --Disseminated (Hepatosplenomegaly, lymphadenopathy (~60%))
  --Isolated bone marrow involvement (~25%) or isolated extranodal (skin>>)
  -- Autoimmune disease but no evident lymphoma at diagnosis (~10-20%)
- ~1/3 have autoimmune disorders (RA, ITP, SLE, vasculitis..)
- Anemia is very common
- Broad band on electrophoresis in Beta region→ immunofixation to prove it is abnormal gamma

Gamma Heavy chain disease

Histology:

Polymorphous infiltrate (lymphocytes, plasmacytoid lymphocytes, plasma cells, Immunoblasts, eosinophils)





Other plasma cell neoplasms

Plasma cell neoplasms with associated paraneoplastic syndrome	POEMS syndrome TEMPI syndrome (provisional)

(WHO Classification of tumors of hematopoietic and lymphoid tissues, Revised 4th edition)

POEMS syndrome

(**P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal protein, **S**kin changes)

International Myeloma Working Group (IMWG) criteria:

Both mandatory criteria

- Demyelinating polyneuropathy
- Monoclonal plasma cell proliferative disorder (lambda)

Plus at least **one major** criterion :

- Osteosclerotic or mixed sclerotic/lytic lesion visualized on plain films or CT
- Castleman disease
- Elevated serum or plasma VEGF levels (>/= 3-4x upper limit of normal)

Plus at least **one minor** criterion

- Organomegaly
- Extravascular volume overload
- Endocrinopathy
- Skin changes
- Papilledema
- Thrombocytosis

Median survival of 13 years (Mayo) -Progressive polyneuropathy leading cause of death

Dispenzieri A., et al, Blood 2003

POEMS

CASE RECORDS *of the* MASSACHUSETTS GENERAL HOSPITAL

Founded by Richard C. Cabot

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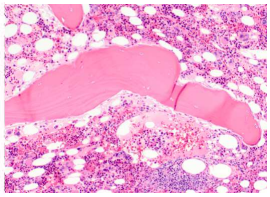
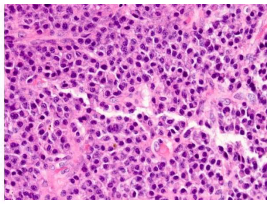
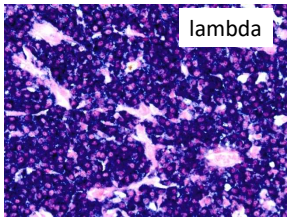
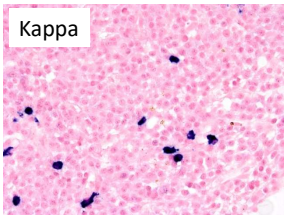
Case 7-2010: A 49-Year-Old Man with Peripheral Neuropathy and Ascites

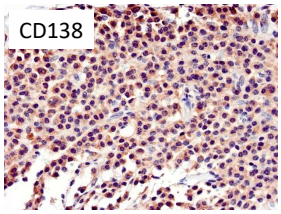
Allan H. Ropper, M.D., Noopur S. Raje, M.D., Tara M. Lawrimore, M.D., Sandra Camelo-Piragua, M.D., and Aliyah R. Sohani, M.D.











TEMPI syndrome

Telangiectasias, elevated **E**rythropoietin and erythrocytosis, **M**onoclonal gammopathy, **P**erinephric fluid collections, and **I**ntrapulmonary shunting.

CASE RECORDS *of the* MASSACHUSETTS GENERAL HOSPITAL

Case 23-2010: A 49-Year-Old Man with Erythrocytosis, Perinephric Fluid Collections, and Renal Failure

Hasan Bazari, M.D., Eyal C. Attar, M.D., Douglas M. Dahl, M.D., Raul N. Uppot, M.D., and Robert B. Colvin, M.D.

PRESENTATION OF CASE

Dr. David B. Sykes (Hematology–Oncology): A 49-year-old man was admitted to this hospital because of erythrocytosis, perinephric collections of fluid, and acute renal failure.

We request that any reader with thoughts about the diagnosis, further evaluation, or treatment contact Dr. David Sykes (dbsykes@partners.org) or any of the authors.

TEMPI syndrome

The TEMPI Syndrome — A Novel Multisystem Disease

Table 1. Characteristics of Patients with the TEMPI Syndrome.*

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Demographic						
Age (yr)	42	36	39	35	56	36
Sex	Male	Female	Female	Male	Male	Male
Year of presentation	2001	2005	1991	1978	1970	2002
Geographic location	Memphis, TN	Antwerp, Belgium	Los Angeles	Manchester, U.K.	Seattle	Indianapolis
Race or ethnic group	White	Belgian	Indian	White	Finnish	Mexican
TEMPI syndrome						
Telangiectasias, most prominent over the face, trunk, arms, and hands	Yes	Yes	Yes	NR	Yes	NR
Erythrocytosis	Yes	Yes	Yes	Yes	Yes	Yes
Hematocrit at presentation (%)	58	64	58	62	66	73
Erythropoietin (mU/ml)						
First measurement	16	50	600	NR	Increased	38
Highest value	>5000	>5000	>5000	>500	Increased	NR
Monoclonal gammopathy	IgG kappa	IgG kappa	IgG kappa	NR	IgG	NR
MGUS	Yes	Yes	Yes	NR	NR	NR
Perinephric fluid between the kidney and the renal capsule, without parenchymal renal cysts	Yes	Yes	Yes	Yes	NR	Yes
Requiring surgical marsupialization	Yes	No	Yes	Yes	No	Yes
Intrapulmonary shunting, microscopic	Yes	Yes	Yes	NR	Yes	NR
Hypoxemia	Yes	Yes	Yes	NR	Yes	Yes
Other						
Venous thrombosis†	Yes	Yes	Yes	NR	NR	NR
Spontaneous intracranial hemorrhage	No	Yes	Yes	NR	NR	NR

* Race or ethnic group was reported by the investigators. MGUS denotes monoclonal gammopathy of unknown clinical significance, and NR not reported.
† Thrombosis involved the internal jugular vein in Patient 1, the cerebral venous sinus in Patients 2 and 3, and the common femoral vein in Patient 3.

Usually IgG k

Sykes D. et al, NEJM 2011

TEMPI syndrome

Complete Responses in the TEMPI Syndrome after Treatment with Daratumumab

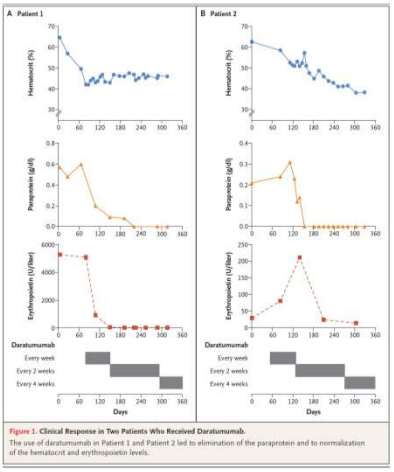


Figure 1. Clinical Response in Two Patients Who Received Daratumumab.
The use of daratumumab in Patient 1 and Patient 2 led to elimination of the paraprotein and to normalization of the hematocrit and erythropoietin levels.

Abnormal plasma cells
And monoclonal gammopathy may be responsible for the syndrome.

The response to the antiCD38 antibody supports the hypothesis above.

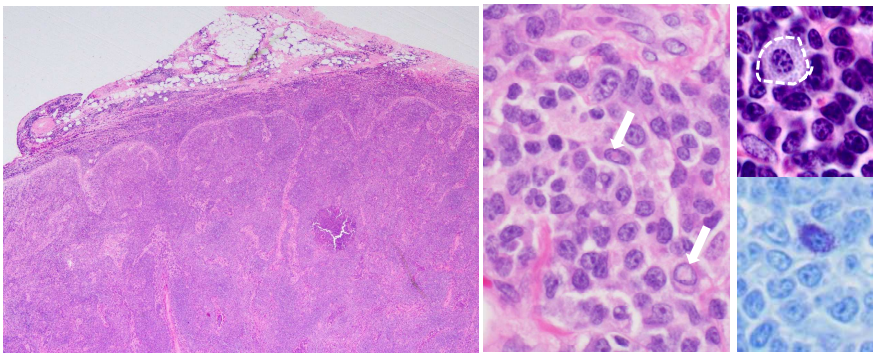
Sykes D. et al, NEJM 2018

Lymphoplasmacytic lymphoma

Neoplasm of small B lymphocytes, plasmacytoid lymphocytes and plasma cells, usually involving the bone marrow* and sometimes lymph nodes and spleen, which does not fulfill criteria for other small B-cell lymphoid neoplasms.

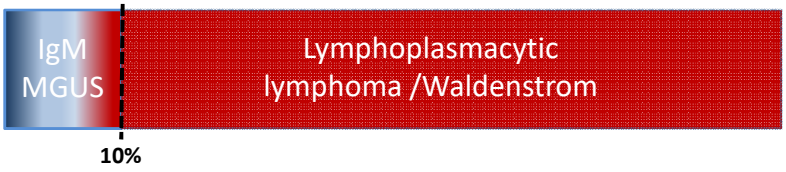
* Waldenstrom Macroglobulinemia ←>LPL in the bone marrow + IgM paraprotein

Immunophenotype: IgM+, CD19+, CD20+, CD22+, CD25+, CD27+, FMC7+, CD5-/+, CD10-, CD23-, CD103-, CD138-



Lymphoplasmacytic lymphoma vs IgM MGUS

Per WHO: <u>At least 10%</u> bone marrow involvement is required to diagnose LPL



No infiltrates on histology (but a clone detected by flow/IGH gene rearrangement/ MYD88 mutation) → **IgM MGUS**

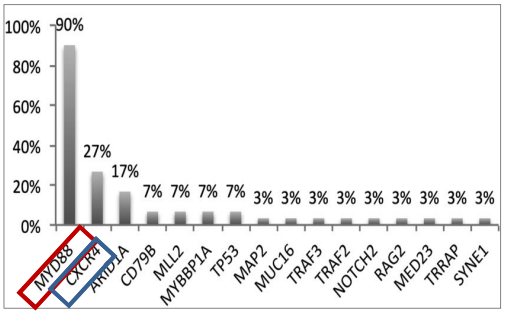
If the patient is symptomatic and symptoms are attributable to the IgM monoclonal protein, then a diagnosis of **IgM-related disorder** may be considered. Clinical correlation is required.

Minimal (<10% cellularity) or otherwise equivocal bone marrow infiltrates: the degree of marrow involvement is less than typically seen in LPL/WM, and is most consistent with **IgM MGUS.**

If the patient is symptomatic and symptoms are attributable to the IgM monoclonal protein, then a diagnosis of **IgM-related disorder or early marrow involvement by LPL/WM** may be considered. Clinical correlation is required.

Lymphoplasmacytic lymphoma genetic landscape

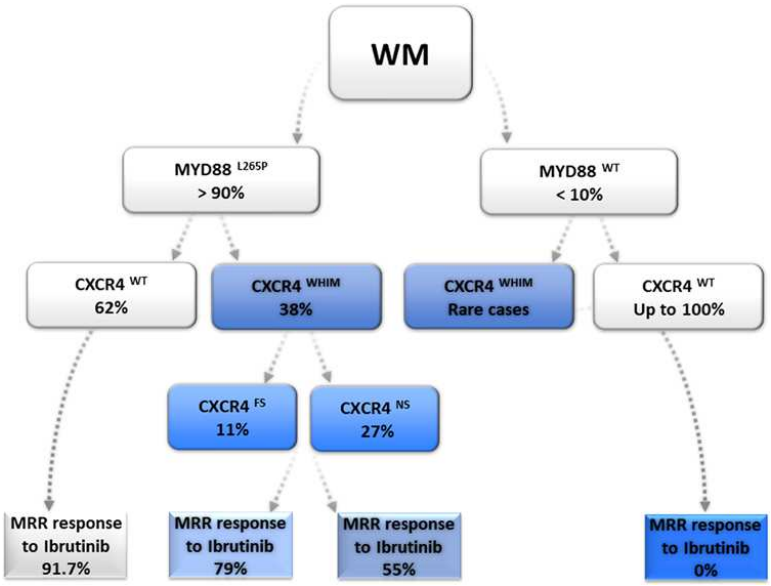
- MYD88 L265P mutation in >90% of cases
- CXCR4 C-terminus nonsense or frameshift mutations in ~30-40% of cases



MYD88 p.L265p :
~ 90-97% of WM / LPL
~ 69% of primary cutaneous leg-type DLBCL
~ 50-80% IgM MGUS
~ 38% to 50% of CNS lymphomas, intravascular lymphomas
~ 8-30% ABC type DLBCL
~ 4-9% of MALT lymphomas
~7% of Mantle cell lymphomas
~ 3% of patients with CLL

Ngo VN, Young RM, Schmitz R. Nature. 2011;
Treon et al, NEJM 2012; Hunter Z. et al, Blood 2014;
De Groen R., et al., Haematologica 2019

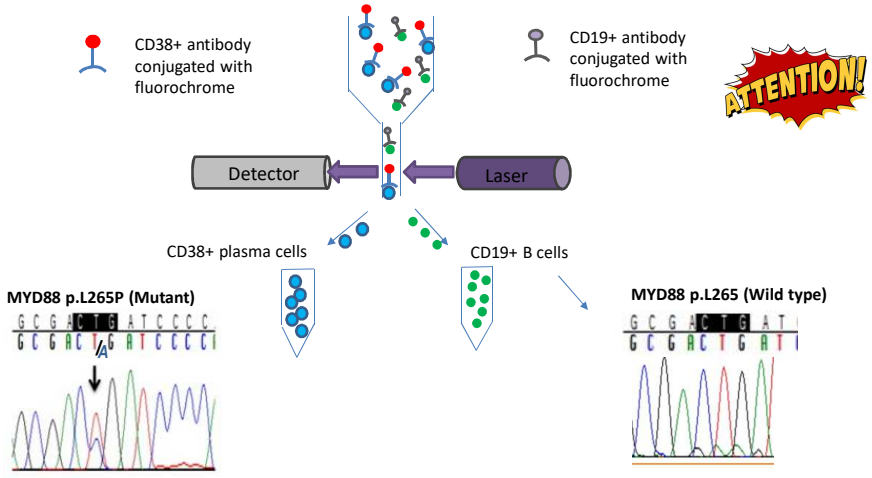
Lymphoplasmacytic lymphoma: mutations predict drug response



Kaise LM., Hunter ZR, Treon S. and Buske, Leukemia 2021

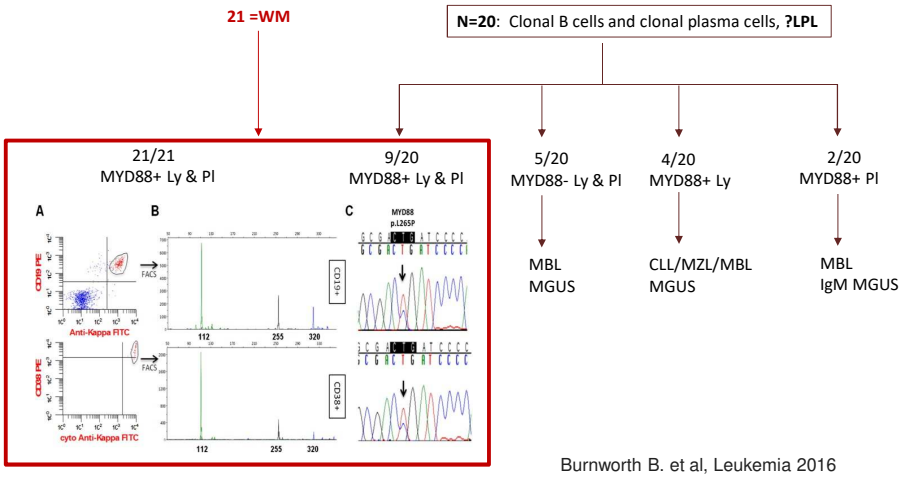
Lymphoplasmacytic lymphoma: lumpers vs splitters

Sorting B cells and plasma cells prior to MYD88 testing



Burnworth B. et al, Leukemia 2016

Lymphoplasmacytic lymphoma: lumpers vs splitters



Burnworth B. et al, Leukemia 2016

Thank you for your attention!