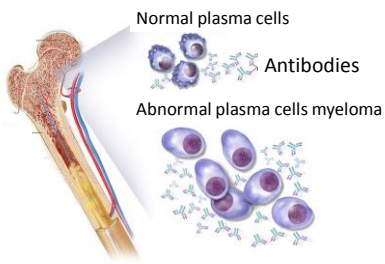
Paraproteinemic Neuropathies
MGUS, Anti-MAG, POEMS,

Dr. Kristine Chapman

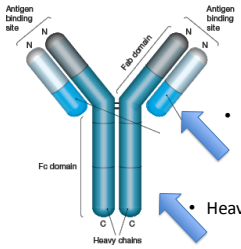
Disclosures

- Research support from Genzyme
- Education Project grants from Grifols

Paraproteins are immunoglobulins that are produced in excess by an abnormal clonal proliferation of B- lymphocytes or plasma cells.



Antibody Structure

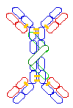


- Light Chains
  - Lambd
  - Kappa
- Heavy Chains

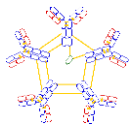
Paraproteinemic Neuropathy

- Monoclonal proteins exist as
  - Heavy chain subtypes (mainly IgG, IgA, IgM)
  - Light chain subtypes (kappa or lambda).

IgG



IgA

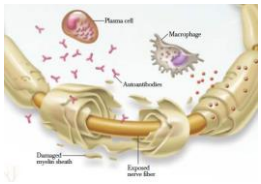


IgM

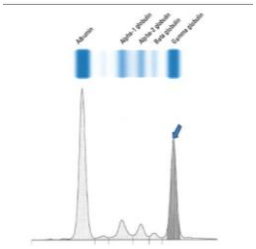
Antibody Associated Neuropathies "The Big Picture"

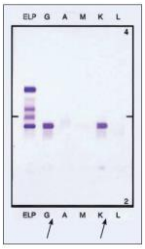
Neuropathies associated with auto-antibodies

- GBS/CIDP
- Paraneoplastic ie anti Hu antibodies
- Monoclonal proteins
  - MGUS
  - Anti-MAG
  - POEMS
  - Amyloid
  - Cryoglobulinemia
  - CANOMAD syndrome



Protein Electrophoresis and Immunofixation





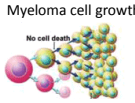
Paraproteins

- Paraproteins are detected in the serum of
  - 1% of the general population
  - 5% over 70 years of age
  - 10% over 80 years of age
- 10% of patients with a chronic sensory motor neuropathy of unknown origin have an associated serum monoclonal gammopathy

Association with Malignancy

- Clonal proliferation may occur in the context of a hematologic malignancy or a pre-malignancy.
- Associated disorders include
  - Multiple myeloma
  - Cryoglobulinemia
  - Lymphoma
  - Amyloidosis
  - Waldenstrom macroglobulinemia
  - POEMS (polyneuropathy, orga- nomegaly, endocrinopathy, M-protein spike, and skin manifestations) syndrome

Myeloma cell growth



Defining Features of Common B-Cell Clonal Disorders

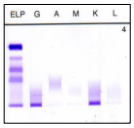
	Asymptomatic		Symptomatic		
	MGUS	Smoldering multiple myeloma	Multiple myeloma	Waldenstrom macroglobulinemia	AL amyloidosis or other clonal protein deposition disease
M-spike	IgG or IgA < 30 g/L	IgG or IgA ≥ 30 g/L	IgG or IgA ≥ 30 g/L	Any IgM monoclonal gammopathy	Any monoclonal gammopathy or abnormal serum free light chain assay results
Bone marrow clonal cell population	< 10% clonal plasma cells	> 10% clonal plasma cells	Any clonal plasma cell population	10% lymphoplasmacytic infiltration	Any clonal plasma cell or B-cell lymphoma population
CRAB criteria*	None	None	At least one	Not a defining feature	May or may not be present
Related organ or tissue impairment	None	None	Hypogammaglobulinemia Occult bone disease Hyperviscosity Cytopenias	Anemia Other cytopenias Neuropathy Hyperviscosity Cryoglobulinemia Retinopathy Fatigue	Any fibril induced end-organ dysfunction: • Renal (often proteinuria) • Cardiac • Liver • Nerve (peripheral or autonomic) • Soft tissue

*Calcium: > 0.25 mmol/L above the upper limit of normal or > 2.75 mmol/L
Renal insufficiency: creatine >173 mmol/L
Anemia: Hb 20 g/L below the lower limit of normal or Hb < 100 g/L

M. Brigden BCMJ Feb 2014

Case #1- MGUS

- 73 year old African-Canadian man with a 9 month history of numbness and paresthesias in the feet
- Sensory level to the mid-shin
- Weakness of EHL 4+/5, otherwise normal
- Absent ankle jerks
- NCS: sensory-motor axonal neuropathy



- Serum Immunofixation shows Ig G kappa (1 g/dL)

What to do About MGUS?

"MGUS"

Monoclonal Gammopathy of Uncertain Significance

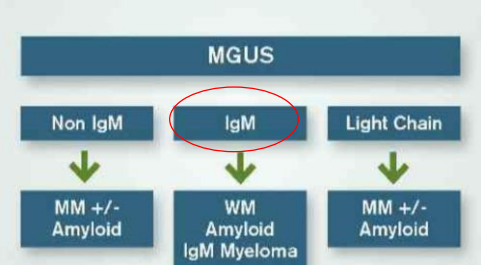
- MGUS is a common, age-related condition.
- Accumulation of plasma cells from a single abnormal clone without proliferation of malignant cells.
- Usually asymptomatic.

- Three criteria define MGUS:
  - A monoclonal paraprotein band < 30 g/L (3 g/dL)
  - Plasma cells < 10 % on bone marrow
  - No evidence of end organ damage: "CRAB"
    - Hypercalcemia,
    - Renal insufficiency related to the paraprotein
    - Anemia
    - Bone lesions

- (If they have a neuropathy, they are already "of interest" – not incidentally found)

MGUS → Transformation

- Each year 1% of people with MGUS go on to develop a more serious disorder



Risk Stratification in MGUS

- Monoclonal protein > 1.5 g/dL
- Ig A or Ig M (non IgG)
- Abnormal Free Light Chain ratio
  - Kappa-Lambda ratio < 0.26 or > 1.65 is abnormal

  - 1 risk factor: Low risk 5% progression in 20 years
  - 2: Intermediate risk 20% progression in 20 years
  - 3: High risk 60% progression in 20 years

MGUS Work UP

- Hx and physical (fatigue, bone pain)
- CBC
- Routine chemistry (calcium, GFR, creatine, albumin, LFT)

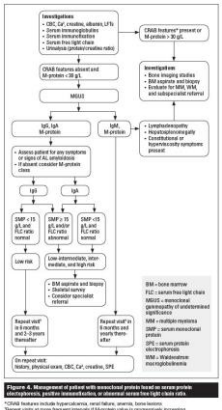
- SPEP /UPEP
- Immunofixation
- Serum-free light chain assay
- (Urinalysis - protein/creatine ratio)

- Skeletal survey
- Hematology review → bone marrow biopsy

- Advise GP to see **twice annually** initially, low risk can reduce to annual f/u.
- For intermediate and high risk the hematologist will often follow as well
- Only repeat imaging or bone marrow analysis if suspicion of progression.

Testing strategy

- Characterize the neuropathy: NCS/EMG
- CSF analysis – elevated protein, cytology for leptomeningeal infiltration (in presence of lymphoma)
- Nerve and muscle biopsy – exclude infiltrative neoplasm, vasculitis or AL
- VEGF for POEMS
  - Vascular endothelial growth factor



MGUS Screening

MGUS treatment

- Rx if assoc. with CIDP

- Treat neuropathic pain
- ETOH moderation
- Remain active
- Foot checks
- OT/PT as needed

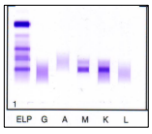
M. Brigden, BC Medical Journal, vol. 56 2014

CASE 2: Anti-MAG Neuropathy

- Fit 49 yr ER physician, runs weekly
- Bilateral burning and numbness in soles of feet, sensation of bunched socks, tripping, bilateral hand tremor with some difficulty suturing lacerations in ER

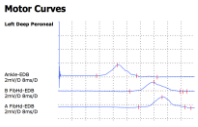
Case 2: Anti MAG Neuropathy

- PE:
  - Mild wasting of hand and intrinsic foot muscles, distal weakness
  - Absent ankle jerks
  - Impaired position sense in toes, vibration loss in toes and hands
  - Ataxic gait
  - Tremor.
- DX: sensorimotor PN presenting with distal weakness and sensory findings
- Lab: CBC, FBG, B12 normal.
- Monoclonal IgM kappa band 15.2 g/L



Electrodiagnostic Findings

- Long distal latencies



Nerve	Lat	Dist	Amp P-P	Amp O-P	Amp%	Area	Stimulus Intensity	Temp	CV
	ms	mm	mV	mV	%	ms*mV	mA	C	m/s
Deep Peroneal Motor Left									
Ankle - EDB	**13.9**	**90.0**	**1.75**	**1.54**		**8.6**	**99.0**		
B FibHd-Ankle	**26.0**	**310**	**1.39**	**1.35**	**-12.3**	**9.6**	**99.0**		**25.6**
A FibHd-B FibHd	**29.4**	**70.0**	**1.57**	**1.45**	**7.4**	**9.3**	**99.0**		**20.6**

Case 2: DADS with IgM paraproteinemia

- Positive anti-MAG assay at Athena

- RX: Rituxamib
- 2 year later – function excellent running 30 km/wk , hand tremor and manual dexterity improved continues to work as ER physician
- Persistent neuropathic pain in extremities improved with neuropathic pain treatment

DADS Phenotype

"Distal Acquired Demyelinating Symmetric"

- Increased prevalence in men, age > 50
- Predominantly distal sensory loss
- Mild distal weakness
- Hand tremor
- Unsteady gait

- IgM paraproteinemia (present in 2/3)
  -> Anti-MAG antibodies
- Subgroup has an indolent presentation -follow clinically
- Poor response to immunosuppressive
  - Rituximab, PLEX, cyclophosphamide

Case 3 - POEMS

- 56 year-old male
- Feb 2015:
  - Burning dysesthesias. Worse at night
  - Numbness and tingling in feet
  - Slowly progressed over months to below knees
- Nov 2015:
  - Similar symptoms in fingers
  - Hand tremor
- Jan 2016
  - Erectile dysfunction (low testosterone)

Neurological exam

- Normal cranial nerves.
- Strength:
  - 4+ weakness on EHL and toe extensors
- Sensory examination
  - Decreased temperature, pinprick, and light touch to mid tibia and elbow
  - Absent vibration at the ankles
- Mild postural tremor in hands
- Unsteady tandem gait. Negative Romberg.

Previous Investigations

- CBC: thrombocytosis
- Elevated fasting Glucose.
- Normal protein electrophoresis.

- Electrolytes, kidney function, TSH, ANA, ANCA, ENA, RF, Vitamin B12, syphilis
- Previous NCS: reported as axonal PN.

EMG/NCS

Sensory Nerve Conduction Studies

Nerve	Lat ms	Dist mm	Amp uV	Stim Intensity mA	Temp C	CV m/s
Palmars Sensory Right						
MidPalm - Wrist	1.85	80.0	6.4	16.7		43.2
UlnPalm - Wrist	1.64	80.0	3.7	13.2		48.8
Superficial Peroneal Sensory Left						
LatCalf - DrsFoot	--	120	--	27.9		
Superficial Radial Sensory Right						
SnffBox - Forearm	2.15	100	6.9	38.3		46.5
Sural Sensory Left						
PostLeg - Lat Mal	--	120	--	39.2		
Sural Sensory Right						
PostLeg - Lat Mal	--	120	--	32.1		

Motor Nerve Conduction Studies

Nerve	Lat	Dist	Amp P-P	Amp O-P	CV
	ms	mm	mV	mV	m/s
Deep Peroneal Motor Left					
Ankle - EDB	29.8	90.0	--	--	
Median Motor Left					
Wrist - APB	5.21	70.0	2.9	2.4	
Elbow-Wrist	12.0	240	2.5	2.0	35.3
Median Motor Right					
Wrist - APB	5.33	70.0	4.7	3.7	
Elbow-Wrist	11.7	218	4.5	3.5	34.2
Peroneal Tib Ant Motor Left					
Fib Hd - Tib Ant	5.69	115	1.95	1.33	
PopFoss-Fib Hd	10.1	96.0	1.39	0.90	21.8
Tibial Motor Left					
Ankle - Abd hal	8.74	90.0	0.80	0.75	
Pop Fossa-Ankle	24.0	355	0.72	0.54	23.3
Ulnar Motor Left					
Wrist - ADM	4.00	70.0	14.3	10.2	
Bl. elbow-Wrist	8.86	195	9.3	5.8	40.1
Ab. elbow-Bl. elbow	12.1	130	9.0	5.9	40.1

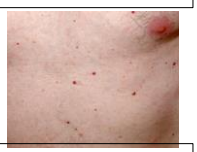
Demyelinating neuropathy but axonal Involvement more common than CIDP

EMG Findings

Muscle	Interpretation	Spontaneous Activity Fib	Spontaneous Activity PSW	Notes
Left L5	NORMAL	0/3	0/3	
Left Gastrocnemius med	ACTIVE DENERVATION	0/3	1/3	
Right FDI	NORMAL	0/3	0/3	
Right Vastus lat	NORMAL	0/3	0/3	
Right Tibialis posterior	NORMAL	0/3	0/3	
Right Gastrocnemius med	ACTIVE DENERVATION	0/3	2/3	
Right Tibialis anterior	NORMAL	0/3	0/3	

Skin Changes

- On general exam:
  - Cherry red angiomas in chest
  - Leg discoloration



Endocrine Changes

- Erectile dysfunction→ recent diagnosis of hypogonadism, on hormone replacement

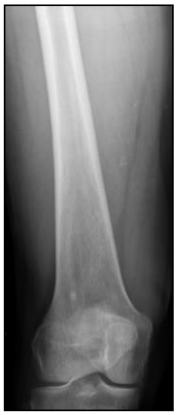
More labs

- Serum Proteins
  - Normal Ig levels
  - Small band (approx. 1.2 g/L) in the fast gamma region.
  - Immunofixation: monoclonal IgA lambda
  - Free Light Chains normal
  - Kappa/Lambda ratio normal
- Hormones
  - Testosterone low
  - Cortisol N
  - Prolactin elevated

Skeletal survey

- No destructive bone lesions
- Sclerotic focus on distal right femur interpreted as a “small bone island”

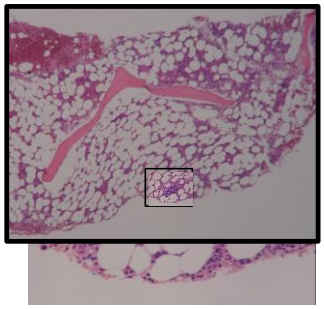
Bone lesions often mis-called without clinical context

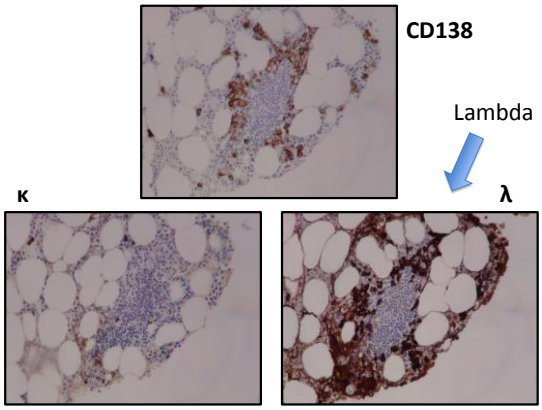


Abdominal US

- Splenomegaly
- No hepatomegaly or lymphadenopathies

Bone Marrow Biopsy





P
- Polyneuropathy

O
- Organomegaly: splenomegaly

E
- Endocrinopathy: hypogonadism, impaired fasting glucose

M
- M-protein: IgA Lambda

S
- Skin: cherry red angiomas, skin discoloration

POEMS syndrome

- Papilledema
- Extravascular Fluid Overload
- Sclerotic Bone Lesions
- Thrombocytosis or polycythemia

P
E
S
T

- Respiratory dysfunction
- Increased risk of thrombosis

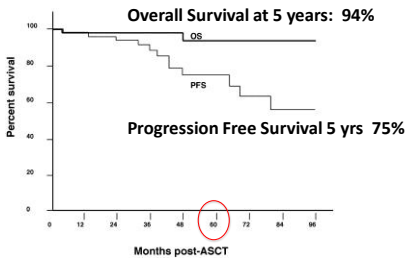
Elevated VEGF

- The cytokine VEGF correlates best with disease activity and is markedly increased in POEMS
- Increases vascular permeability, targets endothelial cells, and is important in angiogenesis.
- A plasma VEGF level of 200 pg/mL or greater has a specificity of 95% and sensitivity of 68% for POEMS

Autologous Stem Cell Transplant

- Higher chance of hematologic complete response
- Associated with significant PN improvement :
  - No need of wheelchair, improvement in NIS and mRS
  - Initial improvement by 3 months, max at 3 years
- No correlation between severity of PN and VEGF levels at baseline
  - But VEGF response to treatment associated with hematological and neurological response

Kaplan –Meier Survival Curve for POEMS Following Autologous Stem Cell Transplant



Anita D'Souza et al. Blood 2012;120:56-62

D'Souza et al Blood 2012

Case 3: Before POEMS Dx

- Received 3mo IVIG and oral steroids
  - Improvement in pain.
  - Worsened strength

POEMS Treatment

- Autologous stem cell transplant

Conclusion

- Paraproteinemic neuropathy: characterized by the presence of homogenous immunoglobulin in serum.
  - If malignancy is identified, target treatment to neoplasm
- Most cases are MGUS
- Anti MAG neuropathy –> treat if disabling; rituximab
- POEMS syndrome→ autologous stem cell transplant
- Multidisciplinary collaboration needed!

Paraproteinemic Neuropathy

Hematologic Disorder	Most Common Monoclonal Protein Type	Peripheral Neuropathy Phenotype	Electrodiagnostic Phenotype
Immunoglobulin M–monoclonal gammopathy of undetermined significance (IgM-MGUS)	IgM kappa	Distal large fiber sensory predominant neuropathy with sensory ataxia	Demyelinating with prolonged distal latencies
Waldenström macroglobulinemia	IgM kappa	Distal large fiber sensory predominant neuropathy with sensory ataxia	Axonal greater than demyelinating (with prolonged distal latencies)
Multiple myeloma	IgG more often than IgA	Length-dependent sensory, sensorimotor, or motor neuropathy	Axonal
Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome	IgG or IgA, lambda	Sensorimotor polyradiculoneuropathy (chronic inflammatory demyelinating polyradiculoneuropathy [CIDP]-like)	Demyelinating
Immunoglobulin light chain (AL) amyloidosis	Lambda	Sensorimotor peripheral neuropathy with prominent autonomic involvement	Axonal

Mauermann, CONTINUUM. October 2014.