Approach to Neuropathy

Manisha Kak Korb, MD

Neuromuscular Assistant Professor

UC Irvine

Disclosures

- I receive honoraria from Biogen for speaking at physician and patient events, as well as for attending advisory boards.

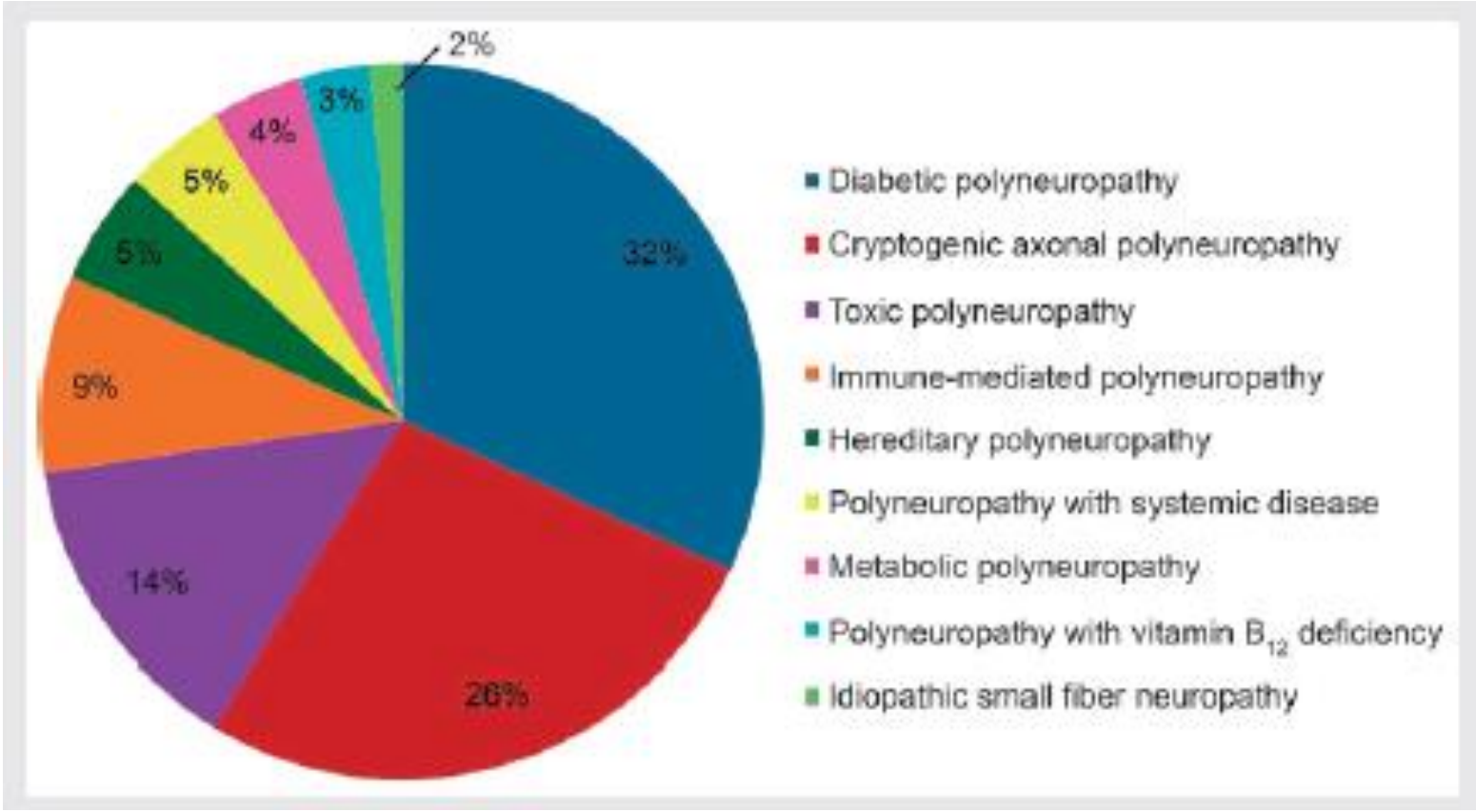
Overview

- Discuss types and patterns of neuropathy
- Discuss diagnostic approach and procedures
- Review treatment methods
- Cases

Peripheral Neuropathy

- Very common in neurology practice!
- Prevalence increases with age;>30% in people over age 80
- > 200 etiologies
- 20-40% remain idiopathic
- Progression to non-ambulation or amputation is uncommon in distal sensory polyneuropathy

Prevalence of Subtypes



Pattern

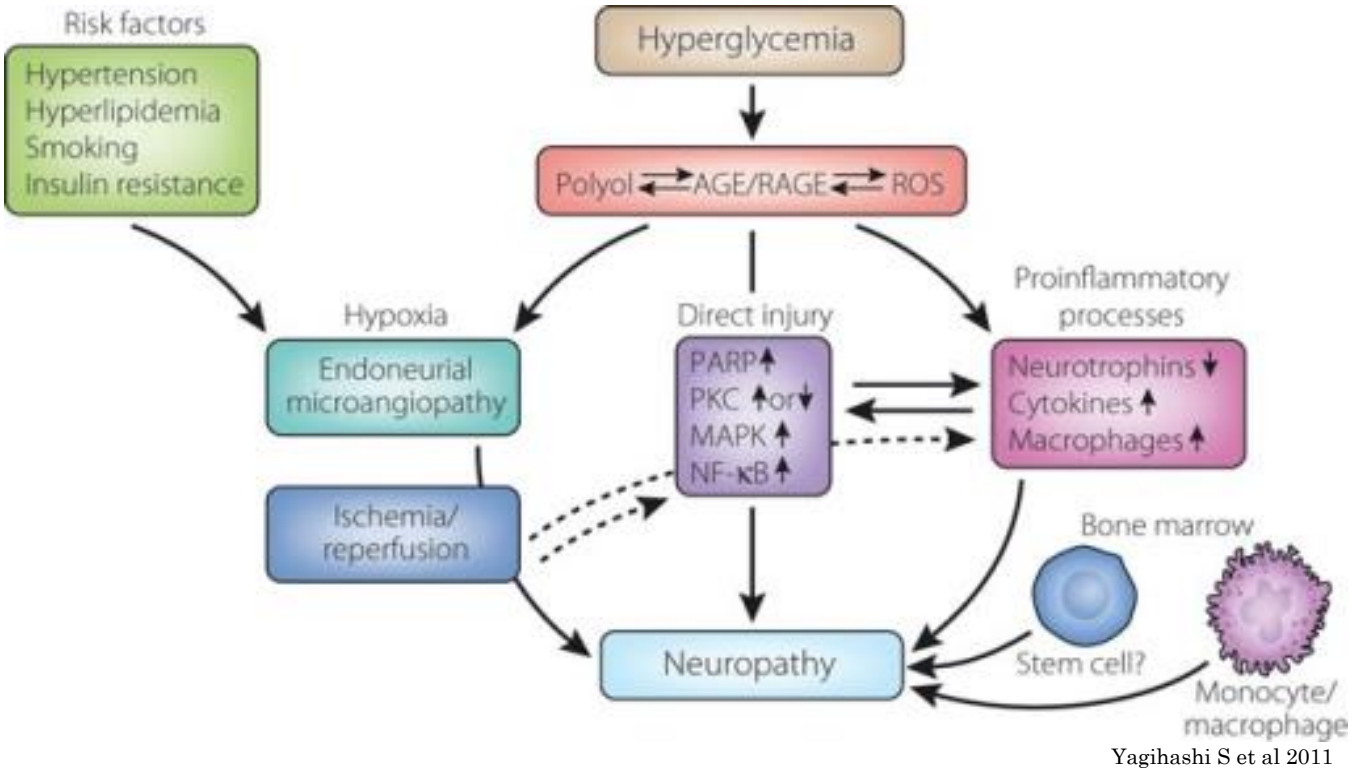
- Sensory, motor, sensorimotor
- Axonal, demyelinating, nodal
- Length-dependent or non-length dependent
  - Non-length dependent: neuronopathy*, multifocal (mononeuritis multiplex), polyradiculopathy, polyradiculoneuropathy
- Small or large fiber
- Hereditary or acquired

- *Neuronopathies: injury to motor or sensory cell bodies (AHC or DRG)

Axonal Polyneuropathies

- Peripheral nerves depend on metabolic state of anterior horn cells and dorsal root ganglion cells, as well as effective axon transport
- Axon transport: vital for axonal nutrition and support for its organelles and proteins
- Gene mutations can be in cell migration, anterograde and retrograde transport, cytoskeletal protein folding, and neurofilament organization

Diabetic Neuropathy



Yagihashi S et al 2011

Chronic hyperglycemia triggers polyol pathway, advanced glycation end-product (AGE) formation, excessive release of cytokines, activation of protein kinase C (PKC), oxidative stress.

Axonal Polyneuropathies

Acute/ Subacute	Chronic
AMAN (GBS)	Diabetes
Porphyria	Thyroid
Infection (HIV, lyme, leprosy, diptheria, hep C)	Alcohol
Drugs (dapsone, nitrofurantoin, vincristine)	Idiopathic (esp in elderly)
Toxins (arsenic, thallium)	CMT 2
Vasculitis (Sjogren's, PAN, SLE, RA)	Amyloid (hereditary)
Paraneoplastic	Hereditary sensory neuropathies
Infiltration (sarcoid, lymphoma/ leukemia)	Adrenomyeloneuropathy
Amyloid (acquired)	Friedreich ataxia
Critical illness	NARP (neuropathy, ataxia, and retinitis pigmentosa)

Demyelinating Neuropathies

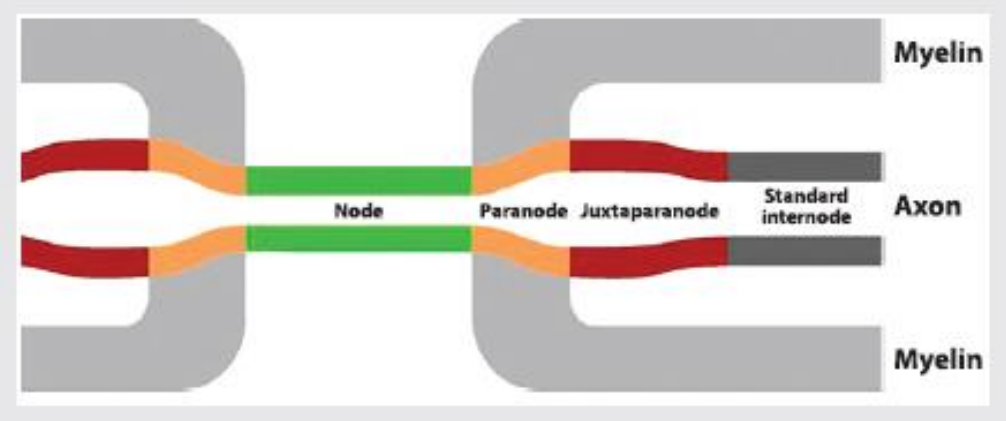
- Schwann cells produce myelin sheath around nerves
- Demyelination → current leakage through exposed section of axon→ hinders action potential propagation
- Hereditary demyelinating neuropathies a/w genes encoding structural myelin proteins
- Acquired demyelinating neuropathies usually target gangliosides; mediated through cellular or humoral mechanisms
- Blood-nerve barrier is less well formed at the nerve roots, DRG, and terminal nerve twigs

Demyelinating Neuropathies

Acute/ Subacute	Chronic
AIDP	CIDP
Multifocal motor neuropathy	Paraprotein related (esp with IgM, anti-MAG)
Paraprotein related (esp with IgM, anti-MAG)	CMT 1, 4, x
Diphtheria	Hereditary neuropathy with liability to pressure palsies (HNPP)
Toxic (amiodarone, arsenic)	Adrenoleukodystrophy, adrenomyeloneuropathy
	Mitochondrial neurogastric encephalomyopathy (MNGIE)

Nodopathies

- Aka channelopathies
- Some toxic, metabolic, and immune mediated neuropathies target nodal region of nerves



- Mechanism: impaired ion channel function → conduction block without structural axonal or myelin injury

Nodopathies cont…

- Examples: AMAN, Miller Fisher, GBS or CIDP associated with abs to nodal antigens, MMN, tetrodotoxin/ ciguatoxin
- AMAN typically has rapid onset of weakness and decline in CMAP amplitudes, but also rapid resolution of clinical and NCS changes
- AMAN associated with GM1 and GD1a abs which are on the nodal axolemma

Hereditary Neuropathies

- ~200 neuropathy related genes identified, but majority of patients ultimately do not get genotyped

- Charcot Marie Tooth
  - Most common cause of hereditary neuropathy
  - Consider checking CMT panel if positive family history, early onset symptoms, pes cavus/ hammer toes, extremely slow NCS conduction velocities
  - Type 1 (AD), 3 (Dejerine Sottas), X (x-linked), some 4 (AR) are demyelinating. Type 2 is axonal AD.

- Fabry's
  - Lysosomal storage disorder
  - Enzyme replacement therapy available

Small Fiber Neuropathy

- 1/3 considered idiopathic
- Most common cause: abnormal glucose metabolism
- Other causes: amyloid, Fabry, Sjogren's, toxic

- Manifestations: burning pain, impaired sweating, impaired cutaneous vascular control, orthostatic intolerance

Clinical Approach: History

- What are the symptoms?
- What is the time course? (acute/subacute/chronic, progressive, stepwise, monophasic, relapsing)
- What fiber types are involved? (motor, sensory, small fiber, autonomic)
- What is the pattern? (distal, proximal, multifocal, symmetric/ asymmetric)
- What is the nerve pathology? (axonal, demyelinating, mixed)
- Are there systemic findings? (diabetes, cancer, connective tissue disorders, infections, vitamin deficiency, celiac/ IBD, porphyria)
- Are there exposure risks? (environmental exposure, occupational history, history of chemo/ prescription drugs, recreational drugs/ EtOH)
- Is there family history? (AD vs AR vs X-linked)

Clinical Approach: Exam

- Sensory loss (check all modalities) and patterns
- Sensory ataxia (pseudoathetosis)
- Weakness (esp in intrinsic foot and hand muscles)
- Muscle atrophy
- Diminished reflexes
- Foot ulcers and deformities (pes cavus, hammer toes)
- Hypertrophic nerves

Red Flags

- Acute/ subacute onset
- Rapid progression
- Non-length dependent
- Associated dysautonomia
- Associated systemic disease
- Motor > sensory involvement

Diagnostic Testing

- Blood work, NCS/EMG, spinal tap, nerve biopsy, skin biopsy, imaging, Qsweat/ autonomic testing, genetic testing, nerve/ muscle ultrasound

- **Routine labs:** B12, MMA, glucose, SPEP with IFE

- **Additional labs, if clinically indicated**: HbA1c, 2 hr oral glucose tolerance test, folate, TSH, vitamin B1, B6, copper, UPEP, ANA, RF, ssa/ssb, ANCA, ESR, CRP, CK, C3/ C4, cryoglobulins, hep B/C, HIV, lyme, ACE, anti-ganglioside panel, anti-MAG, paraneoplastic panel, VEGF, gliadin and endomysial ab, CMT genetic panel

Nerve Conduction Study/EMG

- NCS will tell you if it's axonal or demyelinating, severity, distribution (distal/proximal, symmetry, upper/lower extremity)
  - Only assesses large fiber myelinated nerves
- EMG will tell you if there's a neurogenic vs myopathic process, chronicity, severity, distribution
- Repeating a NCS can show progression/ improvement/ changes
- NCS is not necessarily needed in a stable long standing neuropathy with minimal morbidity

Nerve Biopsy

- Last resort test
- Useful if suspect vasculitis: subacute, multifocal, aggressive, systemic comorbidities
- Usually we use sural or superficial peroneal nerve, and can do concomitant muscle biopsy of peroneus brevis muscle at same site. Also may do superficial radial nerve.

Skin Biopsy

- Punch biopsy usually done in distal leg and thigh
- Helps confirm existence of small fiber neuropathy, but not the cause
- Diagnostic if intraepidermal nerve fiber density <5% for age and gender matched controls

Other Biopsies

- Minor salivary gland (lip): for seronegative Sjogrens
- Lymph node: sarcoidosis
- Small bowel: celiac disease
- Cardiac, fat pad, rectal: amyloid

Autonomic Testing

- Qsweat (ie. QSART): quantitative sudomotor axon reflex test:
  - cholinergic sympathetic function
- HR response to deep breathing and valsalva maneuver:
  - cardiovagal function (parasympathetic); baroreflex
- Tilt table:
  - adrenergic function (sympathetic)

Nerve Ultrasound

- High resolution US can be used to assess nerve dysfunction – higher resolution than MRI for superficial peripheral nerves!
- Can identify fibrosis, pseudoaneurysm, neuroma, bony compression, callous formation over nerve, etc
- Entrapment neuropathies have hypoechoic (dark) focal nerve enlargement near the site of entrapment

Treatment

- Largely depends on underlying etiology
- Toxic: remove offending agent (ie. alcohol or chemo)
- Metabolic: treat derangement (ie. diabetes or thyroid disease)
- Vitamin deficiency related: supplement deficient vitamin
- Immune-mediated neuropathies: treat with steroids (except not in GBS), IVIG, plasma exchange, steroid-sparing agents (such as azathioprine, cellcept)
- Paraneoplastic and paraprotein related: treat underlying malignancy/ plasma cell dyscrasia
- Hereditary: genetic counseling, ERT if relevant, manage symptoms
- Idiopathic: manage symptoms

Symptom Management

- Neuropathic pain meds (gabapentin, pregabalin, duloxetine, nortriptyline, amitriptyline, lidocaine patch, topical ointments, carbamazepine)
- Tramadol, NSAIDs, low dose narcotics – but try to avoid narcotics if possible!
- PT/OT
- Ambulatory assist devices (walker, cane, AFO)
- Integrative rehab: massage therapy, acupuncture, TENS, yoga, tai chi
- Foot care and podiatry for ulcer prevention
- Regular exercise and avoiding a sedentary lifestyle

Therapeutic Effect of Exercise

- Exercise has anti-inflammatory effects that can reduce circulating levels of inflammatory markers like TNF and CRP, increase anti-inflammatory cytokines and T-regulatory cells
- Exercise improves BMI, oral glucose tolerance, serum cholesterol in diabetics (Smith 2006)
- 1 year of exercise increased IENFD in DM patients without neuropathy, and in those with impaired glucose tolerance with neuropathy (Singleton 2014; Kluding 2012)
- A RCT in DM patients showed long term aerobic exercise training (4 hrs/wk at 50-85% max HR) prevented onset and modified natural history of diabetic polyneuropathy (Balducci 2006)

Case 1

- 67 yo F who presents with progressive numbness that started in her fingers and then spread to her thighs and down her legs over the last several weeks.
- She has profound loss of vibratory sense in all 4 limbs, impaired JPS, patchy pinprick/ temperature loss, pseudoathetosis in UEs, areflexia, and ataxic gait.
- DDx:
  - Axonal polyneuropathy
  - Sensory ganglionopathy
  - Freidrich's ataxia
  - Spinocerebellar ataxia

Nerve / Sites	Rec. Site	Onset Lat	Amp	Velocity	Temp.
		ms	µV	m/s	°C
L Sural					
calf	Post ankle	NR			32.4
R Sural					
calf	Post ankle	4.2	3	39	32.9
L Median - Digit II					
Wrist	Dig II	3.2	7	52	33.8
L Ulnar – Digit V					
Wrist	Dig V	NR			33.6
L Radial – Snuff					
Forearm	Wrist	2.8	5	54	34.4

Nerve	F wave latency
	ms
L median	28
L ulnar	26
L peroneal	46
L tibial	51

Nerve / Sites	Muscle	Latency	Amplitude	Velocity	Temp.
		ms	mV	m/s	°C
L Median – APB					
Wrist	APB	2.4	9.4		33.6
Upper arm	APB	6.65	9.2	54	33.5
L Ulnar – ADM					
Wrist	ADM	2.7	4.9		33.6
B.Elbow	ADM	5.9	4.2	62	34
A.Elbow	ADM	7.1	4.1	59	34.1
L Peroneal					
Ankle	EDB	5.5	5.0		33.6
Below fibula		9.6	4.9	48	33.5
L tibial					
Ankle	AHB	5.4	6.2		33.6
Popliteal fossa		8.7	5.5	47	34

Needle EMG							
	Spontaneous			Volitional MUAPs			
Muscle	**IA**	**Fibs/PSW**	**Fasc**	**Dur.**	**Amp**	**Poly**	**Recruit**
L. TA	Nml	-	-	Nml	Nml	Nml	Nml
L. Med gastroc	Nml	-	-	Nml	Nml	Nml	Nml
L. VL	Nml	-	-	Nml	Nml	Nml	Nml
R deltoid	Nml	-	-	Nml	Nml	Nml	Nml
R biceps brachii	Nml	-	-	Nml	Nml	Nml	Nml
R triceps brachii	Nml	-	-	Nml	Nml	Nml	Nml
R FCR	Nml	-	-	Nml	Nml	Nml	Nml
R FDI	Nml	-	-	Nml	Nml	Nml	Nml

Case 1 Work up

- SSA/SSB, B6 negative or normal
- CXR with hilar mass → small cell carcinoma on biopsy
- Paraneoplastic panel: positive for Anti-Hu antibodies

Case 2

- 59 yo M who presents with progressive numbness and weakness for the last 6 months. It started with paresthesias in his feet and moved up his calves, and recently he has also developed paresthesias in his fingertips.
- He has lost 10 lbs

- DDx:
  - Axonal polyneuropathy
  - CIDP
  - Small fiber neuropathy

Nerve / Sites	Rec. Site	Onset Lat	Amp	Velocity	Temp.
		ms	µV	m/s	°C
L Sural					
calf	Post ankle	NR			
R Sural					
calf	Post ankle	NR			
L Median - Digit II					
Wrist	Dig II	4.5	3	32	33.8
L Ulnar – Digit V					
Wrist	Dig V	3.7	5	34	33.6
L Radial – Snuff					
Forearm	Wrist	4.1	5	37	34.4

Nerve	F wave latency
	ms
L median	NR
L ulnar	NR
R peroneal	NR
R tibial	NR
L peroneal	NR

Nerve / Sites	Muscle	Latency	Amplitude	Velocity	Temp.
		ms	mV	m/s	°C
L Median – APB					
Wrist	APB	8.4	6.4		33.6
Upper arm	APB	15.65	1.2	24	33.5
L Ulnar – ADM					
Wrist	ADM	6.7	4.9		33.6
B.Elbow	ADM	14.9	2.2	22	34
A.Elbow	ADM	20.1	2.2	19	34.1
R Peroneal					
Ankle	EDB	9.5	3.0		33.6
Below fibula		20.6	1.0	18	33.5
R tibial					
Ankle	AHB	12.4	4.2		33.6
Popliteal fossa		24.72	0.5	21	34
L Peroneal					
Ankle	EDB	10.35	3.2		33.6
Below fibula		23.65	2.4	19	33.5

Needle EMG							
	Spontaneous			Volitional MUAPs			
Muscle	**IA**	**Fibs/PSW**	**Fasc**	**Dur.**	**Amp**	**Poly**	**Recruit**
L. EHL	Incr	2+	-	Incr	Incr	2+	Sev reduced
L. TA	Incr	1+	-	Incr	Incr	2+	Sev reduced
L. Med gastroc	Incr	1+	-	Incr	Incr	1+	Sev reduced
L. VL	Nml	0	-	Incr	Incr	1+	Sev reduced
L glut med	Nml	0	-	Nml	Nml	Nml	Mildly reduced
R FDI	Incr	1+	-	Incr	Incr	2+	Mildly reduced
R EIP	Incr	0	-	Nml	Incr	Nml	Mildly reduced
R pronator teres	Nml	0	-	Nml	Nml	Nml	Mildly reduced
R biceps brachii	Nml	0	-	Nml	Nml	Nml	Normal
R deltoid	Nml	0	-	Nml	Nml	Nml	Normal
R TA	Incr	1+	-	Incr	Incr	1+	Mod reduced
L biceps brachii	Nml	0	-	Nml	Nml	Nml	Normal

Case 2 Work up

- NCS/EMG overall c/w chronic sensorimotor demyelinating polyneuropathy with secondary axonal features. Dx: CIDP.
- Spinal tap: CSF protein 400mg/dl, 2 wbc
- HIV, SPEP, anti-MAG ab negative, VEGF positive
- Skeletal survey: sclerotic lesion in L3 vertebral body
- Biopsy: osteosclerotic myeloma
- Referred to heme/ onc for chemo/ RT

Thank you!