Peripheral polyneuropathy

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Polyneuropathy: dysfunction or disease of many or all peripheral nerves

(D. Preston “Electromyography and Neuromuscular Disorders)

Pathologic classification of neuropathic disorders:

1. Neuronopathies (pure sensory or pure motor or autonomic):
a. Sensory neuronopathies (ganglionopathies)
b. Motor neuronopathies (motor neuron disease)
c. Autonomic neuropathies
2. Peripheral neuropathies (usually sensorimotor):
a. Myelinopathies
b. Axonopathies
❖Large- and small-fiber
❖Small-fiber
a. Nodopathies

Sensory fibers:

- Large fibers – mediate vibration, proprioception and touch
- Small fibers – convey pain and temperature sensations

Negative: lack of function

Positive: abnormal function or overfunctioning

Table 26–1. Negative and Positive Symptoms and Signs of Peripheral Nerve Disease

	Negative	Positive
Motor	Weakness Fatigue Hyporeflexia or areflexia Hypotonia Orthopedic deformities (e.g., pes cavus, hammer toes)	Fasciculations Cramps Myokymia Restless legs "Tightness"
Sensory		
Large fiber	Decreased vibration sensation Decreased joint position sensation Hyporeflexia or areflexia Ataxia Hypotonia	"Tingling" "Pins and needles"
Small fiber	Decreased pain sensation Decreased temperature sensation	"Burning" "Jabbing" "Shooting"
Autonomic	Hypotension Arrhythmia Decreased sweating Impotence Urinary retention	Hypertension Arrhythmia Increased sweating

D. Preston "Electromyography and Neuromuscular Disorders"

3-6-10-step clinical approach to neuropathy:

Barohn&Amato; Neurol Clin 31 (2013) 343–361:

1. 3 goals
2. 6 key questions (from the history and physical)
3. 10 phenotypic patterns

Polyneuropathy investigation - goals:

1. Determine anatomic and physiologic locations (based on clinical and electrodiagnostic findings).
2. Determine etiology (see recommended laboratory assessment based on phenotypic patterns).
3. Determine treatment.

(Barohn&Amato; Neurol Clin 31 (2013) 343–361

M. Arnold; Phys Med Rehabil Clin N Am 29 (2018) 761–776)

Barohn&Amato;
Neurol Clin 31 (2013) 343–361

Box 3
Approach to neuropathic disorders: 6 key questions

1. What systems are involved?
   a. Motor, sensory, autonomic, or combinations
2. What is the distribution of weakness?
   a. Only distal versus proximal and distal
   b. Focal/asymmetric versus symmetric
3. What is the nature of the sensory involvement?
   a. Severe pain/burning or stabbing
   b. Severe proprioceptive loss
4. Is there evidence of upper motor neuron involvement?
   a. Without sensory loss
   b. With sensory loss
5. What is the temporal evolution?
   a. Acute (days to 4 weeks)
   b. Subacute (4–8 weeks)
   c. Chronic (>8 weeks)
   d. Preceding events, drugs, toxins
6. Is there evidence for a hereditary neuropathy?
   a. Family history of neuropathy
   b. Skeletal deformities
   c. Lack of sensory symptoms despite sensory signs

Clinical Patterns of Neuropathic Disorders

PATTERN	Weakness: Proximal	Weakness: Distal	Weakness: Asymm	Weakness: Symm	Sensory Symptoms	Severe Proprioceptive Loss	UMN Signs	Autonomic Symps/Signs	Diagnosis
NP1 - Symmetric prox & distal weakness w/sensory loss	+	+		+	+				GBS/CIDP
NP2 - Distal sensory loss with/without weakness		+		+	+				CSPN, metabolic, diabetes, drugs, hereditary, DADS
NP3 - Asymmetric distal weakness with sensory loss		+	+		+				Multiple – vasculitis, HNPP, MADSAM, infection Single - Mononeuropathy, radiculopathy
NP4 - Asymmetric prox & distal weakness w/sensory loss	+	+	+		+				Polyradiculopathy, plexopathy, DLSRP, cancer, idiopathic, infection
NP5 - Asymmetric distal weakness w/out sensory loss		+	+				+/-		+ UMN – ALS/PLS - UMN – MMN
NP6 – Symmetric sensory loss & upper motor neuron signs		+		+	+	+	+		B12/Copper defic; Friedreich's, ALD
NP7 - Symmetric weakness without sensory loss*	+\-	+		+					<u>Prox & Distal</u> SMA <u>Distal</u> Hereditary motor neuropathy
NP8 - Focal midline proximal symmetric weakness*	+ Neck/trunk extensor or + Bulbar + Diaphragm			+ +			+ +		ALS ALS/PLS
NP9 – Asymmetric proprioceptive loss w/out weakness			+		+	+			Sensory neuronopathy (ganglionopathy) CISP
NP10 – Autonomic dysfunction								+	Diabetes, GBS, amyloid, prophyria

*Overlap patterns with myopathy and NMJ disorders

Adapted from Barohn RJ, Amato AA,. Neurol Clin 2013;31(2):343-361

Table 3
Ten phenotypical patterns and recommended laboratory workup

Etiologies	Suggested Laboratory Workup
Pattern 1: Symmetric proximal and distal weakness with sensory loss	
Consider: • Inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome/ acute inflammatory demyelinating polyradiculoneuropathy, chronic inflammatory demyelination polyradiculoneuropathy, and variants) • Confirm diagnosis using published clinical criteria and electrodiagnostic criteria for demyelination[12]	Consider specialty screenings: • Serologies: ◦ *Campylobacter jejuni* ◦ Hepatitis ◦ Influenza ◦ Cytomegalovirus ◦ *Mycoplasma pneumoniae* ◦ Epstein-Barr virus ◦ Human immunodeficiency virus (HIV) ◦ Rapid plasma reagin (RPR) for syphilis ◦ Others • Autoantibodies[19]: ◦ Anti-MAG, anti-sulfatide: neuropathies associated with paraproteinemia ◦ Anti-GM1: Multifocal motor neuropathy, AMAN ◦ Anti-GQ1b: Miller-Fisher syndrome ◦ Others
Pattern 2: Symmetric distal sensory loss with or without distal weakness	
Consider: • Cryptogenic (idiopathic) sensory polyneuropathy • Metabolic disorders[6] ◦ Vitamin deficiencies (B12, folate, thiamine, vitamin E) ◦ Malabsorption: bariatric and gastric surgeries, inflammatory bowel disease ◦ Renal disease ◦ Chronic liver disease ◦ Metabolic syndrome • Drugs[16]: ◦ Neurologic/psychiatric agents: phenytoin, amitriptyline, lithium ◦ Antimicrobials: nitrofurantoin, metronidazole, chloramphenicol, tuberculosis therapies, chloroquine, hydroxychloroquine ◦ Cardiovascular agents: statins, amiodarone, flecainide, hydralazine ◦ Nitrous oxide ◦ Antirheumatic agents: colchicine, gold, leflunomide, methotrexate ◦ Immunomodulators: tacrolimus, interferon-α, ipilimumab, nivolumab, pembrolizumab, bortezomib, others ◦ Antineoplastic therapies: various chemotherapeutic agents, paclitaxel and other taxanes, vinca alkaloids, platinum analogues, doxorubicin, etoposide, ifosfamide, misonidazole ◦ Antinucleosides	Highest yield[18]: • Fasting blood sugar; if negative then glucose tolerance test • Serum B12 with metabolites (methylmalonic acid with/without homocysteine) • SPEP with immunofixation, UPEP, +/− quantitative immunoglobulins Additional laboratory tests to consider: • Erythrocyte sedimentation rate • C-reactive protein • Rheumatoid factor (RF) • Antinuclear antibody (ANA) • Thyroid stimulating hormone with reflexive T4 • Complete blood count with differential • Complete metabolic panel • Serum folate • Heavy metals from serum and/or 24-h urine

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M. Arnold; Phys Med Rehabil Clin N Am 29 (2018) 761–776)

Table 3
(*continued*)

Etiologies	Suggested Laboratory Workup
• Toxinsx[16]: ◦ Alcoholism ◦ Heavy metal toxicity: lead, arsenic, inorganic mercury, zinc, thallium, gold others ◦ Herbicides (dichlorophenoxyacetic acid, Agent Orange, and other deforestation agents) ◦ Organophosphate insecticides/pesticides (parathion, dioxin, others) ◦ Industrial agents: acrylamide, polychlorinated biphenyl, vinyl chloride (used to make polyvinyl chloride plastic and vinyl products) ◦ Solvents: n-hexane (glue sniffing) and other hexacarbons, dry-cleaning solvents, carbon disulfide, perchloroethylene, trichloroethylene, triorthocresyl phosphate, ethylene oxide, styrene, toluene, methyl n-butyl ketone, mixed solvents, and others • Endocrinopathy[6]: ◦ Diabetes mellitus ◦ Thyroid disease ◦ Acromegaly • Hereditary*: Charcot-Marie-Tooth (CMT), amyloidosis and others • Systemic disorders[6]: ◦ Peripheral arterial disease ◦ Monoclonal gammopathy/ paraproteinemia ◦ Amyloidosis ◦ POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin abnormalities) ◦ Sarcoidosis ◦ Collagen vascular diseases ◦ Critical illness	*There is level A evidence for genetic testing in patients with suspected hereditary neuropathy and level C evidence in patents with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype[18]: • Charcot-Marie-Tooth 1A: assay for PMP22 duplication • Hereditary neuropathy with liability to pressure palsies (HNPP): assay for PMP22 deletion • X-linked Charcot-Marie-Tooth: Next-Generation sequencing for connexin-32 • Charcot-Marie-Tooth 2A: Next-Generation sequencing for mitofusin 2
Pattern 3: Asymmetric distal weakness with sensory loss	
Multiple nerves, consider: • Vasculitis (various collagen vascular/ connective tissue disorders)[6]: ◦ Polyarteritis nodosa ◦ Churg-Strauss syndrome ◦ Wegener granulomatosis ◦ Temporal arteritis ◦ Rheumatoid arthritis ◦ Systemic lupus erythematosus ◦ Sjögren's syndrome	• RF, anti-cyclic citrullinated peptide antibody • ANA panel (anti-double-stranded DNA (dsDNA), anti-Sm, SS-A (Ro), SS-B (La), anti-RNP, anti-Jo, anti-centromere, Scl-70, others as indicated) • Anticytoplasmic antibodies: p-ANCA, c-ANCA • Cryoglobulins • Serum complement • Lyme titer

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Table 3
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Etiologies	Suggested Laboratory Workup
○ Scleroderma ○ Cryoglobulinemia ○ Others • HNPP • Multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy • Infectious (leprosy, Lyme, sarcoid, HIV) Single nerves/regions, consider: • Compressive mononeuropathy • Radiculopathy • Herpes zoster focal paresis	• HIV
Pattern 4: Asymmetric proximal and distal weakness with sensory loss	
Consider[3]: • Polyradiculopathy • Radiculoplexus neuropathy (neurogenic amyotrophy) • Meningeal carcinomatosis or lymphomatosis • Sarcoidosis • Amyloidosis • Lyme disease • Hereditary (HNPP, familial) • Idiopathic	• Imaging studies as appropriate • Lyme titer • HNPP: assay for PMP22 deletion • Biopsy, as appropriate
Pattern 5: Asymmetric distal weakness without sensory loss	
With upper motor neuron findings, consider[3]: • Motor neuron disease: ○ Amyotrophic lateral sclerosis (ALS) ○ Primary lateral sclerosis (PLS) Without upper motor neuron findings, consider: • Progressive muscular atrophy (PMA) • Multifocal motor neuropathy (MMN) • Multifocal acquired motor axonopathy (MAMA) • Juvenile monomelic amyotrophy	• Complete blood count, CMP • Thyroid function tests • C-reactive protein • Creatine kinase • Serum copper • Serum B12 with metabolites (methylmalonic acid) • SPEP, UPEP, immunofixation • ANA • RPR; FTA-ABS (treponemal assay antibody *Treponema pallidum*) • HIV • Consider: ○ Lyme titer ○ Anti-GM1 antibody ○ Genetic testing for familial ALS (C9orf72, SOD-1, others) or Kennedy disease ○ Hexosaminidase A
Pattern 6: Symmetric sensory loss and distal areflexia with UMN findings	
Consider[3]: • B12 deficiency • Copper deficiency (including zinc toxicity) • Other causes of combined system degeneration with peripheral neuropathy • Inherited disorders ○ Adrenomyeloneuropathy ○ Metachromatic leukodystrophy	• Serum B12 with metabolites (methylmalonic acid with/without homocysteine) • Serum vitamin E • Serum copper • Serum zinc • RPR; FTA-ABS

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Table 3
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Etiologies	Suggested Laboratory Workup
○ Friedreich ataxia	
*Pattern 7: Symmetric weakness without sensory loss**	
* Some overlap with myopathy and NMJ disorders[3] • Proximal and distal weakness: consider spinal muscular atrophy • Distal weakness: consider hereditary motor neuropathy	• Creatine kinase • Aldolase • Muscle biopsy • Anti-acetylcholine receptor antibodies • Myositis-specific antibodies
*Pattern 8: Focal midline proximal symmetric weakness**	
* Some overlap with myopathy NMJ disorders. Consider[3]: • Neck extensor weakness ○ Isolated neck extensor myopathy ○ Axial myopathy ○ ALS • Bulbar weakness ○ ALS ○ PLS	• Creatine kinase • Aldolase • Muscle biopsy • Myositis-specific antibodies • Consider other studies as listed under pattern 5
Pattern 9: Asymmetric proprioceptive sensory loss without weakness	
Consider[3]: • Sensory neuronopathy (ganglionopathy): ○ Cancer ○ Paraneoplastic syndromes (small-cell lung cancer, lymphoma, multiple myeloma, others) ○ Sjögren's syndrome ○ Idiopathic sensory neuronopathy ○ Cisplatinum and other analogues ○ Vitamin B6 toxicity ○ HIV-related sensory neuronopathy • Chronic immune sensory polyradiculopathy (CISP)	• Routine cancer screenings • Paraneoplastic panel (anti-Hu, others) • Serum B6 • HIV • ANA reflexive panel: anti-dsDNA, anti-Sm, SS-A (Ro), SS-B (La), anti-RNP, anti-Jo, anti-centromere, Scl-70, others as indicated • Anticytoplasmic antibodies: p-ANCA, c-ANCA
Pattern 10: Autonomic symptoms and signs	
Consider: neuropathies associated with autonomic dysfunction[3]: • Hereditary sensory autonomic neuropathy • Diabetes mellitus • Amyloidosis (familial and acquired) • Guillain-Barré syndrome • Vincristine-induced • Porphyria • HIV-related autonomic neuropathy • Idiopathic pandysautonomia	• Fasting blood sugar; if negative then glucose tolerance test • SPEP with immunofixation, UPEP, +/− quantitative immunoglobulins • HIV

Case #1 - Interesting Case from NM:

- 80 yo native New Mexican M
- Rash on extremities, trunk, back x 5-6 years – inconclusive w/up by 2 Dermatologists (2 skin biopsies, some abnormalities but was told no infection).
- Numbness, tingling, paresthesias to b/l distal extremities x 4 years
- Difficulty opening both hands, weakness
- Multiple falls, left foot drop
- PMH: Parkinson's, BPH, spinal stenosis
- PSH: L4-5 decompressive laminectomy (chronic RLE pain since 2014)
- Worked internationally for Health Organization x 30 years
- Largely lived in Mexico, Brazil; last travel outside USA in 2009
- Previous residence also in Florida, Baltimore, California

Physical Exam:

- Neck flexors (R): 5 (L): 5
- Neck extensors (R): 5 (L): 5
- Deltoid: (R): 5 (L): 5
- Biceps: (R): 5 (L): 5
- Triceps: (R): 5 (L): 5
- Wrist extensors: (R): 5 (L): 5
- EDC: (R): 4+ (L): 4+
- EIP 3/5 bilaterally
- FPL and FDP: (R): 5 (L): 4
- Abductor digiti minimi: (R): 2 (L): 2
- First dorsal interosseous: (R): 4- (L): 4-
- Abductor Pollicis Brevis: (R): 4- (L): 4-

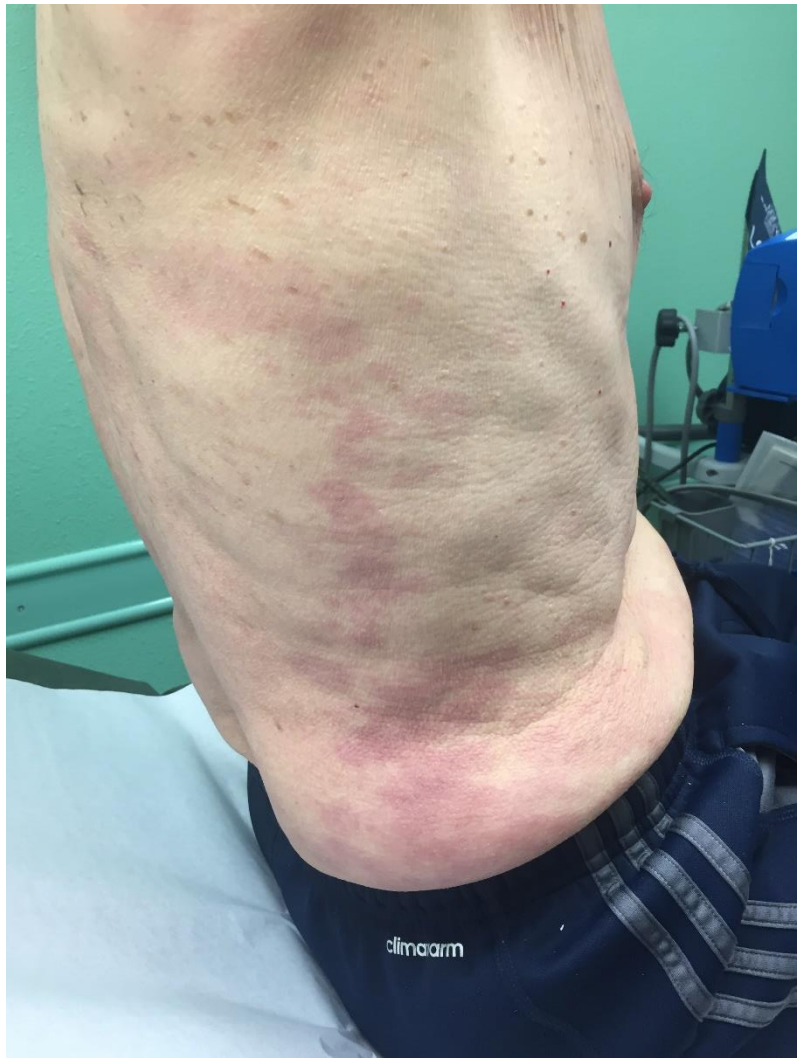
- Abnormal gait due to bilateral feet weakness
- He is able to get up without support from UEs
- He is able to walk on toes bilaterally without any problems
- He has significant difficulty walking on his heels
- He is able to do tandem without any significant loss of balance.
- Tone, muscle bulk are normal in the upper and lower extremities except for atrophy seen in L>R hands

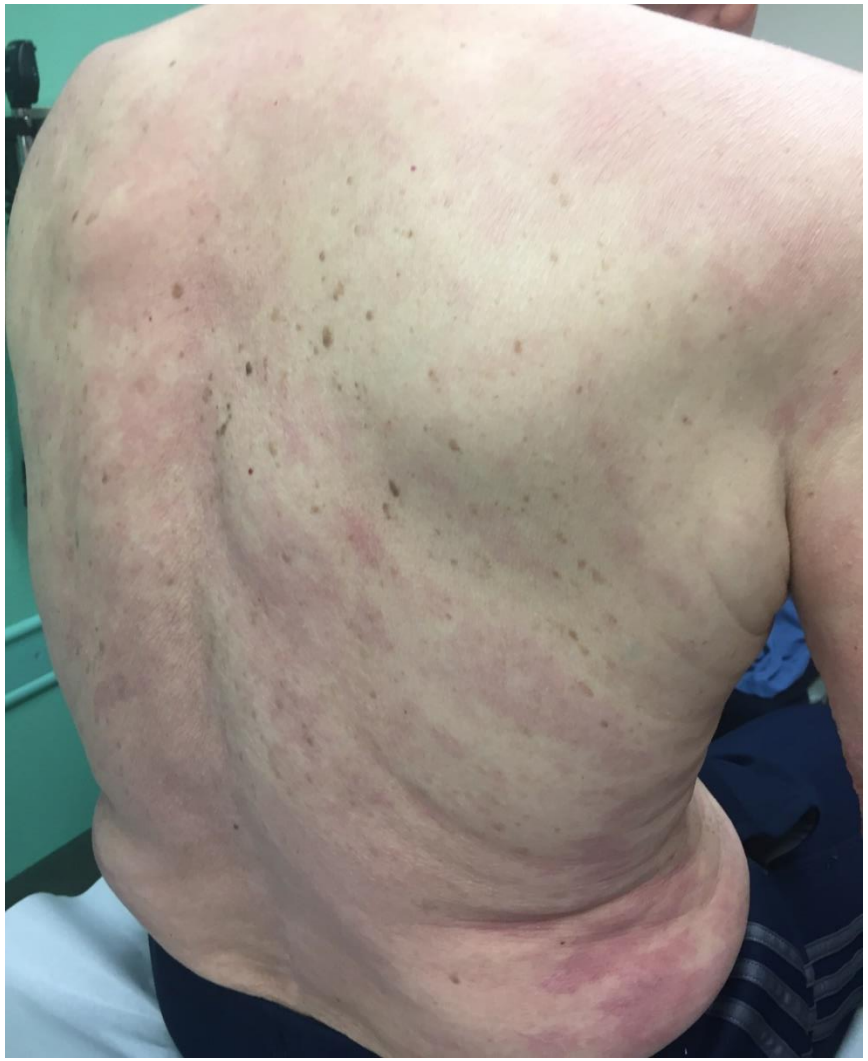
- Hip Flexors: (R): 5 (L): 5
- Quadriceps: (R): 5 (L): 5
- Hamstrings: (R): 5 (L): 5
- Tibialis anterior: (R): 4 (L): 3
- Medial gastrocnemius: (R): 5- (L): 5-
- EHL: (R): 1 (L): 1

- Triceps: (R): 2+ (L): 2+
- Biceps: (R): 2+ (L): 2+
- Brachioradialis: (R): 2+ (L): 2+
- Patellar: (R): 2+ (L): 2+
- Achilles: (R): absent (L): absent
- Hoffman: (R): absent (L): absent
- Babinski: (R): mute (L): mute

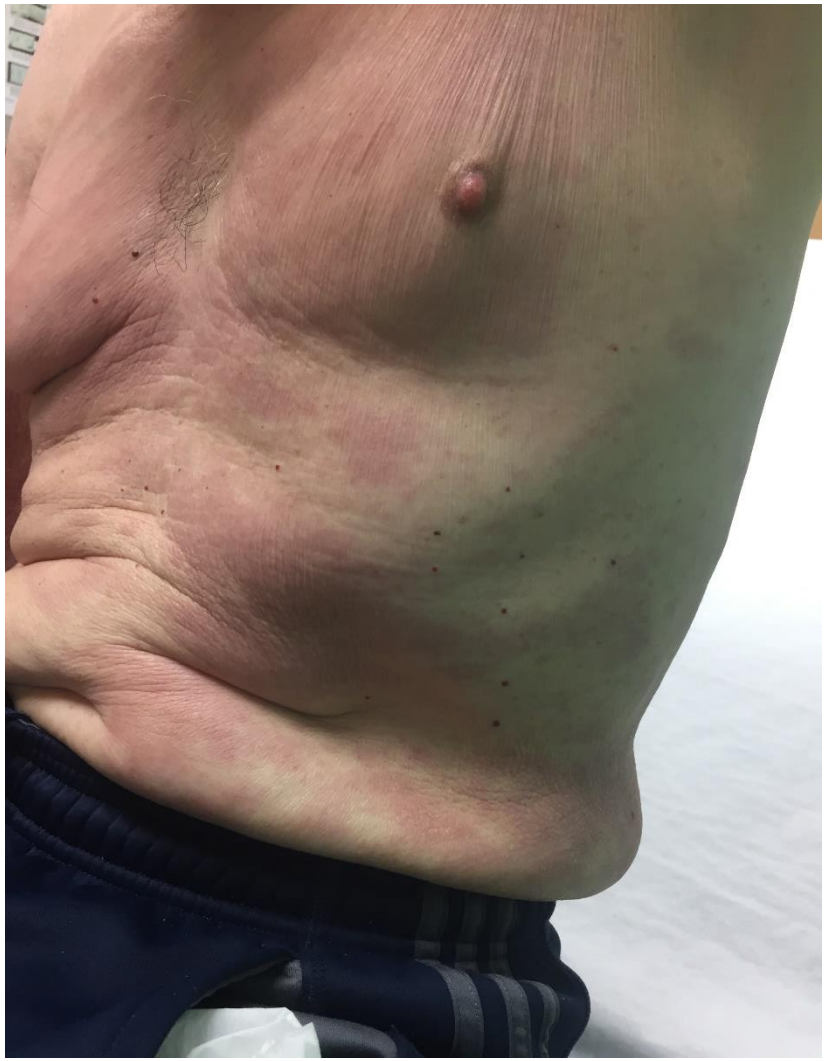
- Vibratory sense:
  - Decreased in bilateral toes and hands
  - Normal in both knees and elbows
- Pinprick sense by dermatomes:
  - Decreased right C8 and bilateral T1
  - Dull bilateral L4 and S1
  - Sharp in bilateral L1, L2, L3, and L5
  - Sharp in bilateral C5, C6, C7 and left C8
- Romberg test is positive

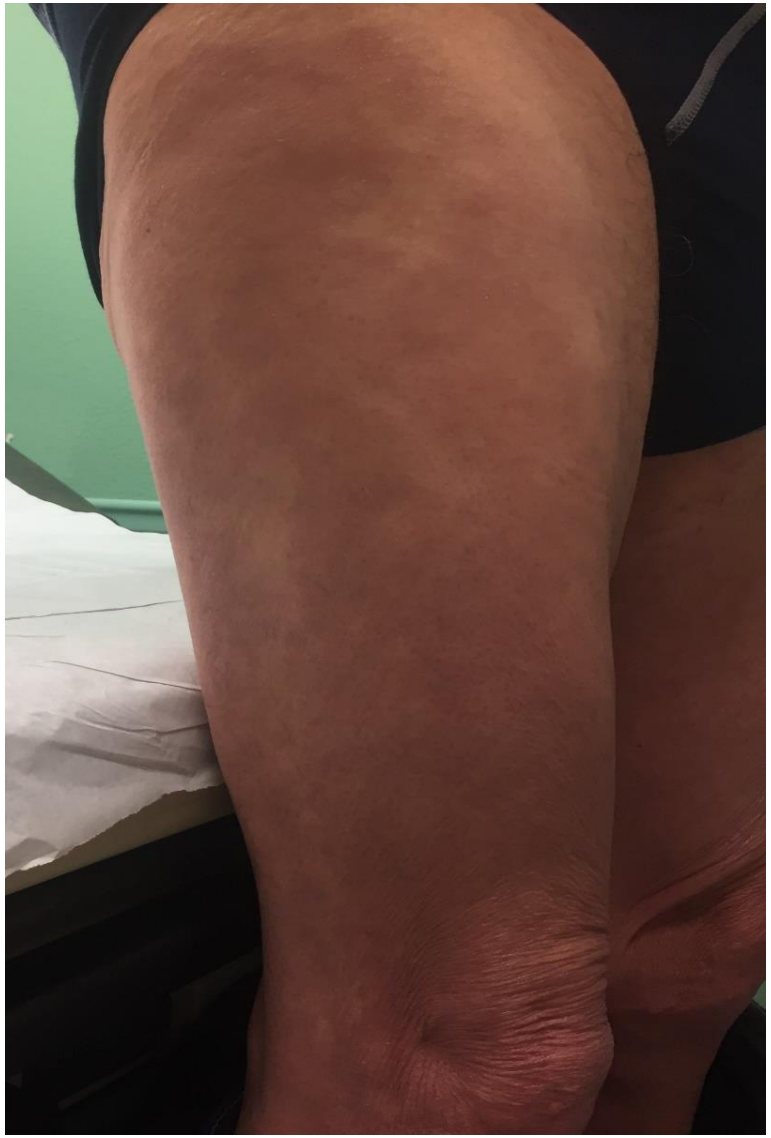
Non-pruritic, non-painful, erythematous, flat macular rash





Non-pruritic, non-painful, erythematous, flat macular rash

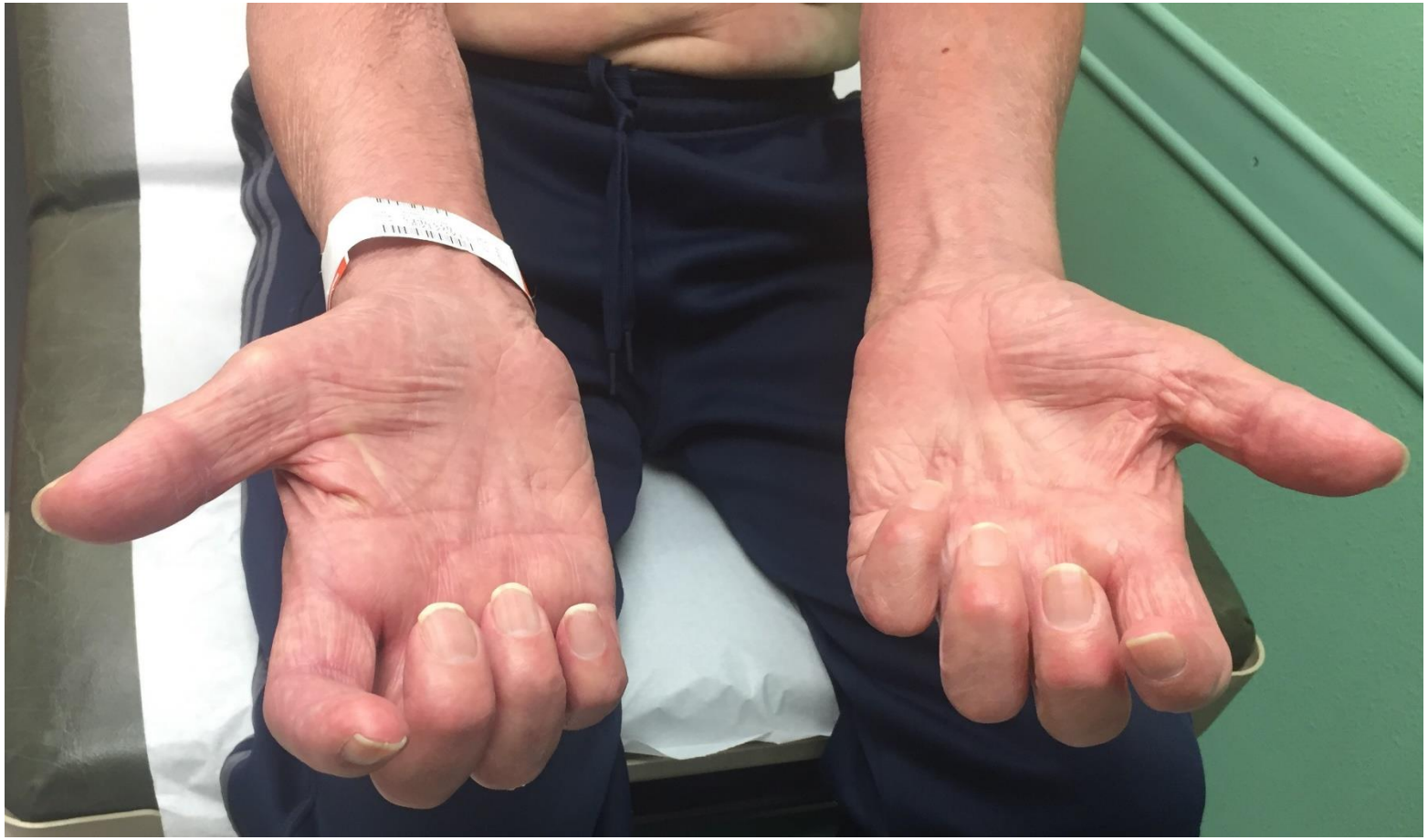




ELECTRODIAGNOSTIC TESTING:

- He had EMG and the nerve conduction study done by large academic center in beginning of 2015 that showed only **old, inactive right L5 radiculopathy** (testing included normal NCS of peroneal motor to EDB, tibial motor to AH, normal sural sensory of 8 microvolts, and normal medial plantar nerve of 3 microvolts). Needle EMG showed large motor unit potentials in right L5 myotome (no fibrillations potentials).
- EMG/NCS of RLE in beginning of 2017 by outside local Neurologist revealed small peroneal and tibial motor amplitudes and unobtainable sural sensory response consistent with **axonal sensorimotor polyneuropathy** (also possible underlying chronic right L5 radic)

Hand contractures, weakness, paresthesias



No responses: b/l median s, ulnar s , superficial radial s
No responses: b/l ulnar m, radial m, R median m
L median m: 7.9 ms; 0.7/0.7 mV; 45 m/s

Needle EMG Examination:

Muscle	Insertion Activity	Spontaneous Activity				Volutional MUAPs					Comments
		Fibs	PSW	Fasc	Other	Effort	Recruit	Dur	Amp	Poly	
Deltoid.L	Normal	None	None	None		Normal	Normal	Normal	Normal	None	
Triceps brachii.L	Normal	None	None	None		Normal	Normal	Normal	Normal	None	
Biceps brachii.L	Normal	None	None	None		Normal	Normal	Normal	Normal	None	Tremulous
1st dorsal interosseous.L	Increased	+3	+3	None		Normal	Reduced	Sl. Incr.	Gr. Incr.	Few	
Extensor indicis proprius.L	Increased	+2	+2	Rare		Normal	Reduced	Sl. Incr.	Gr. Incr.	Rare	
Abductor pollicis brevis.L	Increased	+3	+3	None		Normal	Reduced	Gr. Incr.	Gr. Incr.	Few	
Pronator teres.L	Normal	None	None	None		Normal	Normal	Normal	Normal	None	
Flexor digitorum profundus III & IV.L	Normal	None	None	None		Normal	Sl.reduced	Sl. Incr.	Sl. Incr.	Few	
Cervi Para Low .L	Normal	None	None	None							Unable to fully relax, 1-2 MUAP firing
Cervi Para Low .R	Normal	None	None	None							
Deltoid.R	Normal	None	None	None		Normal	Normal	Normal	Normal	None	Tremulous
Triceps brachii.R	Normal	None	None	None		Normal	Normal	Normal	Normal	None	
Biceps brachii.R	Normal	None	None	None		Normal	Normal	Normal	Normal	None	
1st dorsal interosseous.R	Increased	+3	+3	None		Normal	Reduced	Sl. Incr.	Gr. Incr.	Few	
Extensor indicis proprius.R	Increased	+1	+1	None		Normal	Sl.reduced	Sl. Incr.	Sl. Incr.	Few	
Abductor pollicis brevis.R	Increased	+3	+3	None		Normal	Reduced	Gr. Incr.	Decr.		2 nascent poly MUAPs seen
Pronator teres.R	Normal	None	None	None		Normal	Normal	Normal	Normal	None	
Flexor digitorum profundus III & IV.R	Increased	+1	+1	None		Normal	Sl.reduced	Sl. Incr.	Sl. Incr.	Few	

Needle EMG Examination:

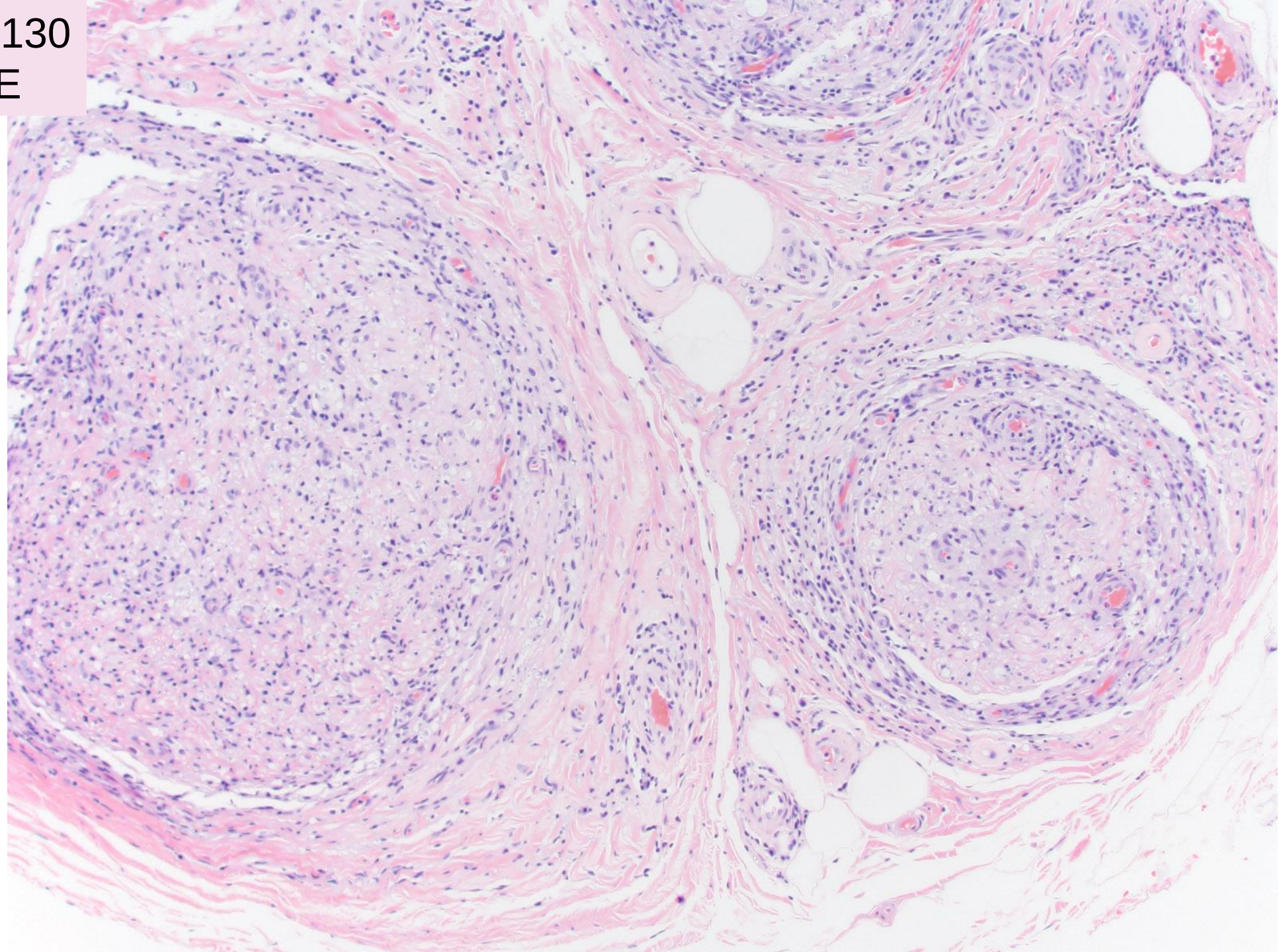
Muscle	Insertion Activity	Spontaneous Activity				Volutional MUAPs					Comments
		Fibs	PSW	Fasc	Other	Effort	Recruit	Dur	Amp	Poly	
Tibialis anterior.R	Increased	1+	1+	None		Normal	Reduced	Gr Incr	Gr Incr	Rare	
Gastrocnemius (Medial head).R	Increased	+1	+1	None		Normal	Sl.reduced	Sl. Incr.	Sl. Incr.	None	
Vastus lateralis.R	Normal	None	None	None		Normal	Normal	Normal	Sl. Incr.	None	
Tensor fasciae latae.R	Normal	None	None	None		Normal	Sl.reduced	Sl. Incr.	Sl. Incr.	Rare	
Gluteus maximus.R	Normal	None	None	None		Normal	Normal	Normal	Normal	None	
Lum Para Low .R	Normal	None	None	None							
Tibialis anterior.L	Increased	3+	3+	None		Normal	Reduced	Sl Incr	Sl Incr	Rare	
Gastrocnemius (Medial head).L	Increased	+1	+1	None		Normal	Sl.reduced	Sl. Incr.	Sl. Incr.	None	
Vastus lateralis.L	Normal	None	None	None		Normal	Normal	Normal	Sl. Incr.	None	
Tensor fasciae latae.L	Normal	None	None	None		Normal	Normal	Normal	Normal	None	
Gluteus maximus.L	Normal	None	None	None		Normal	Normal	Normal	Normal	None	

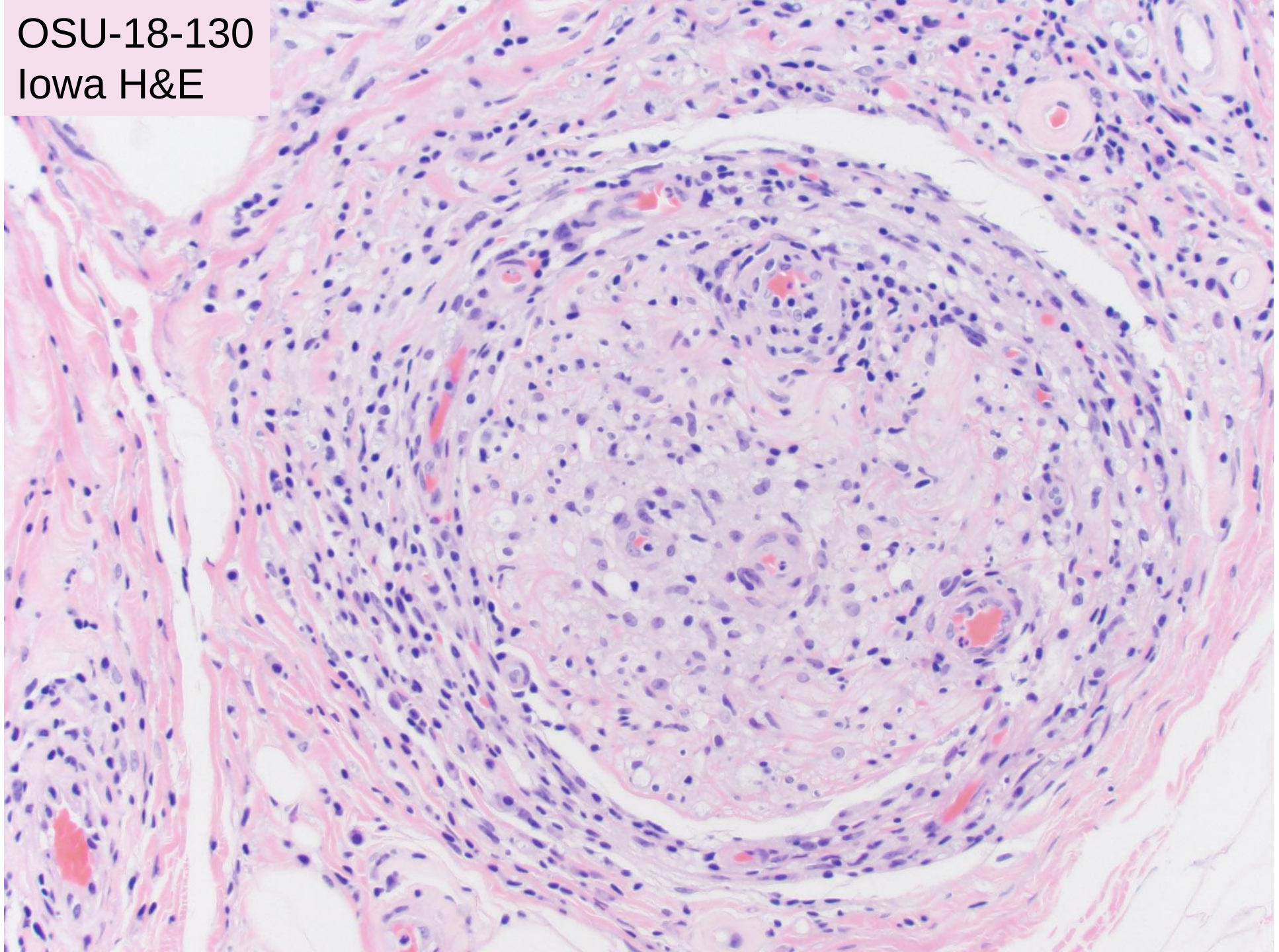
Impression:
This is an abnormal study. This study is also interpreted with electrodiagnostic testing of bilateral upper extremities done on 10/31/2017 (see above). Patient's electrodiagnostic testing of bilateral lower extremities and bilateral upper extremities is consistent with severe, chronic, active, sensorimotor, predominantly axonal polyneuropathy. There appears to be significant progression since previous outside EMG/NCS studies done in April 2015 and January 2017 as mentioned above. Additionally, there is electrophysiological evidence of superimposed chronic right L5 radiculopathy. No electrophysiological evidence of myopathy or significant demyelination was found.

No responses: b/l sural s
No responses: b/l peroneal m EDB, b/l tibial m
R peroneal m TA: 2.5 ms; 2.2/2.1 mV; 44 m/s
L peroneal m TA: 2.6 ms; 0.9/0.6 mV; 40 m/s

OSU-18-130
Iowa H&E

Courtesy of Steven Moore, Iowa

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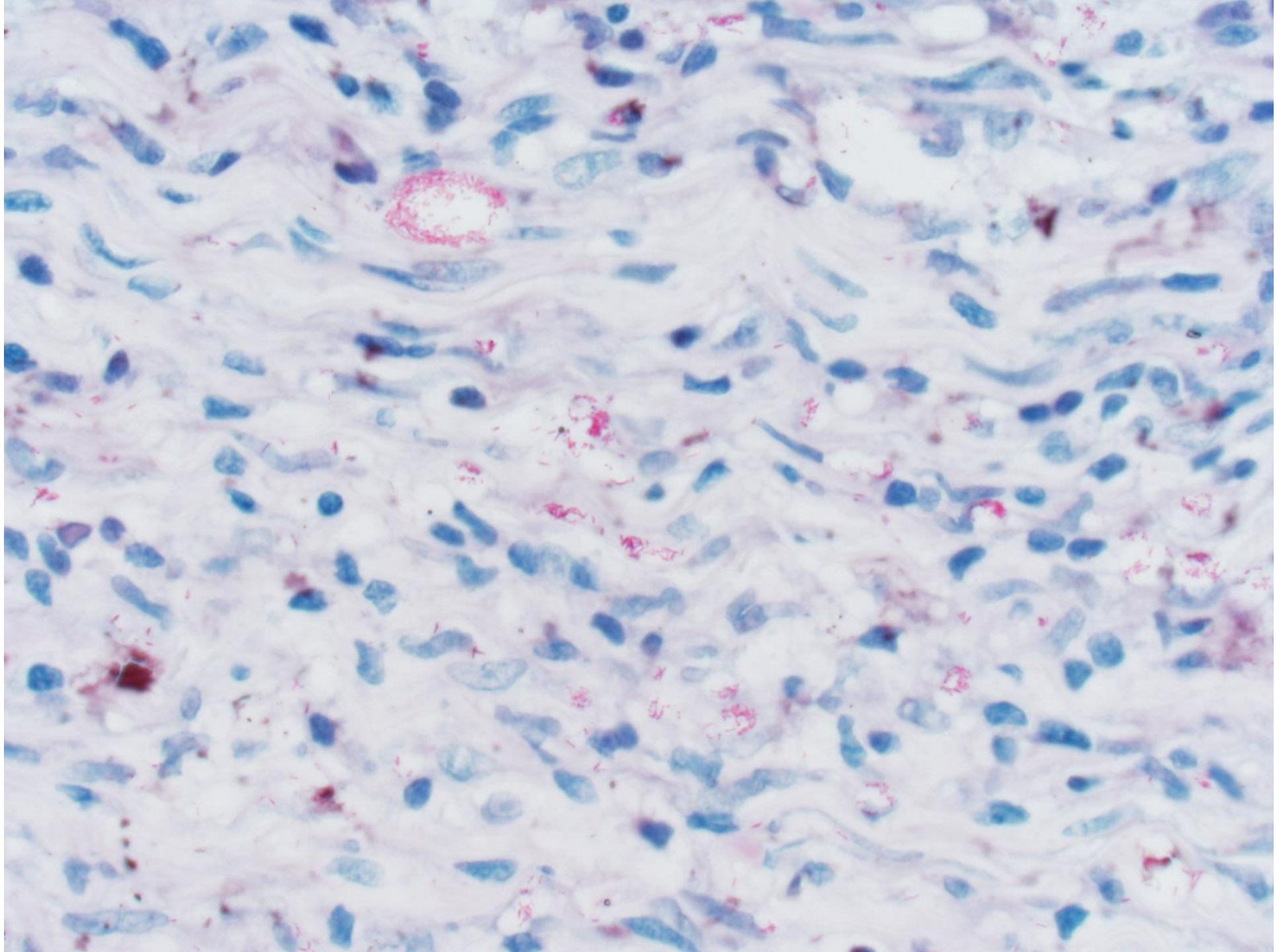

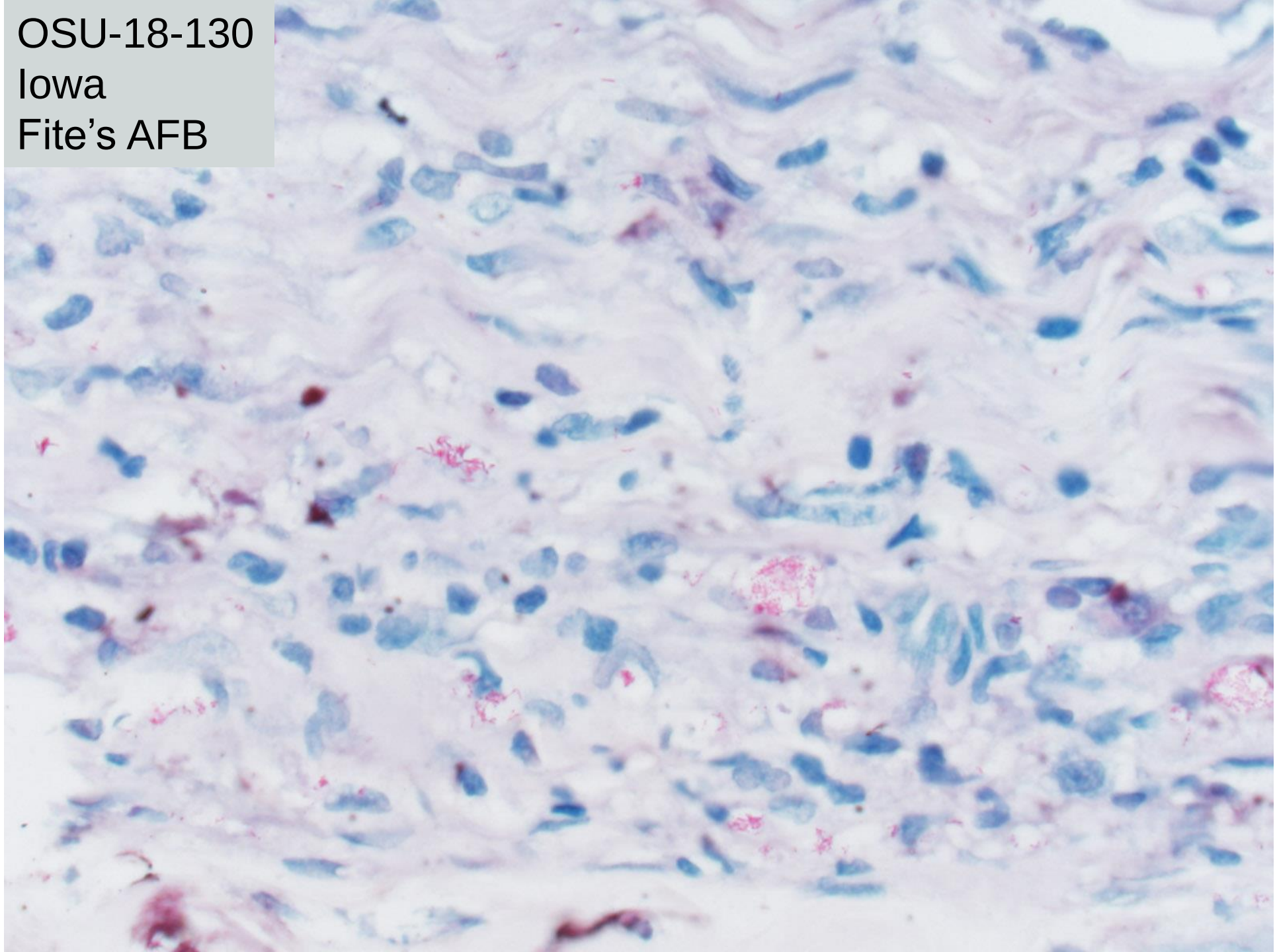
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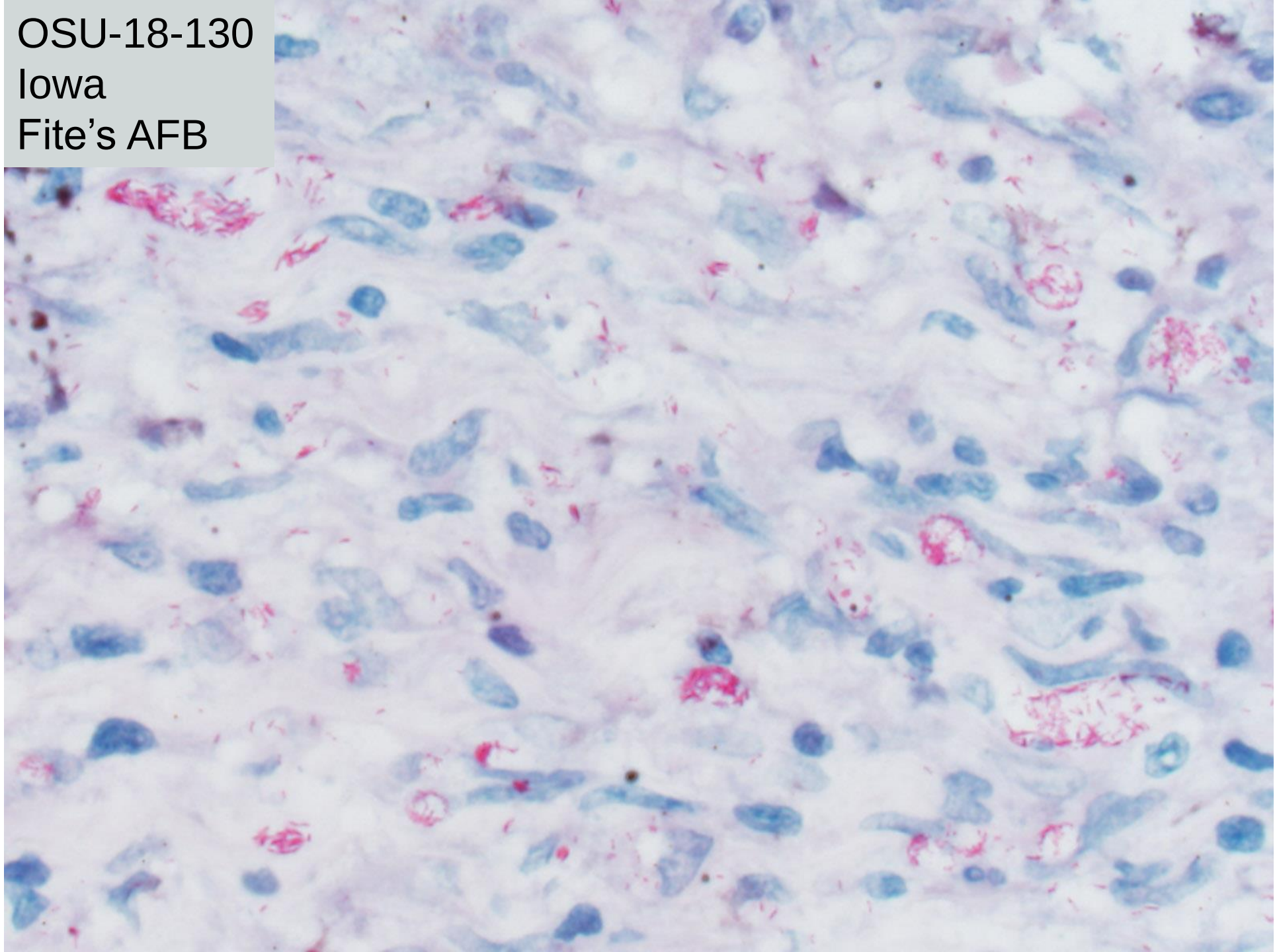
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ELECTRODIAGNOSTIC TESTING IN LEPROSY:

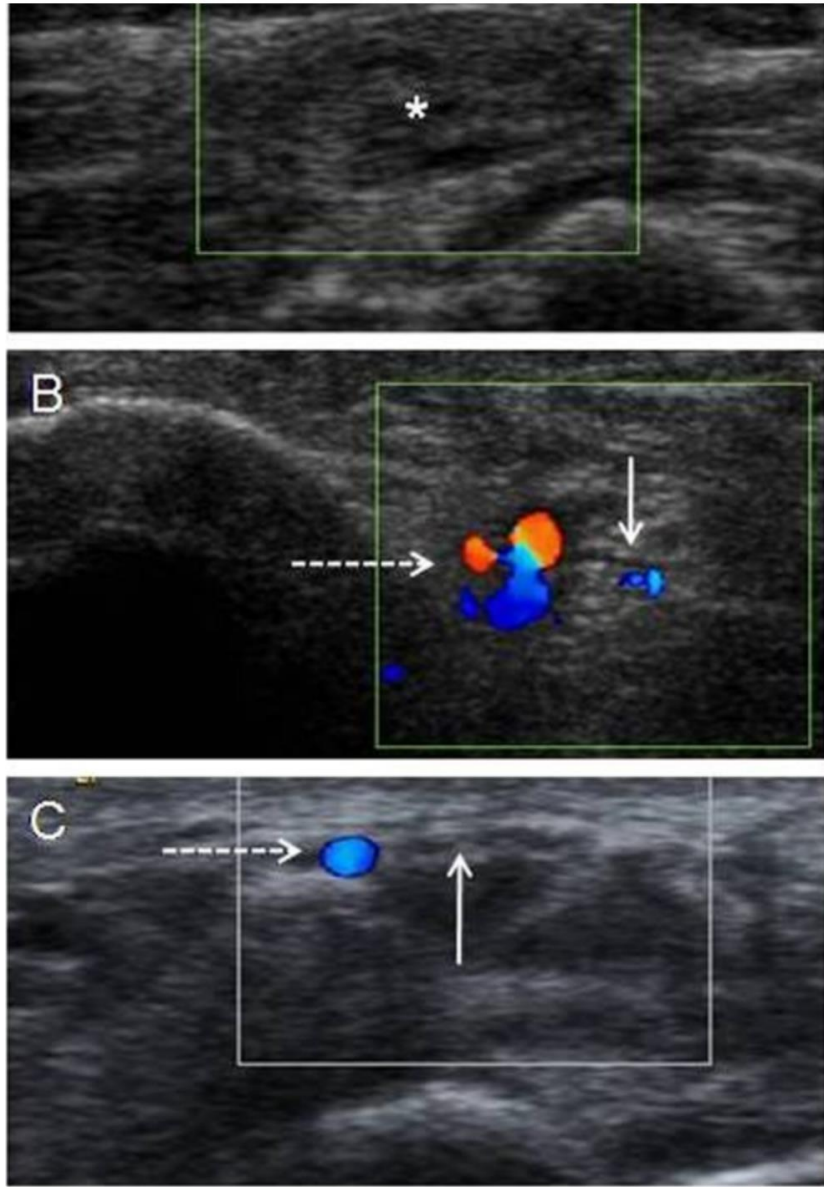
- Nerve conduction studies
  - Early: Evidence of demyelination
    - Distal latencies: Prolonged
    - Conduction velocities
      - Segmental slowing
      - Especially across vulnerable sections: Ulnar nerve at elbow
    - Conduction block: May be found with weakness
  - Later: Axonal loss

PLoS Negl Trop Dis. 2009 Aug 11;3(8):e498. doi: 10.1371/journal.pntd.0000498.

High-resolution sonography: a new technique to detect nerve damage in leprosy.

Jain S[1], Visser LH, Praveen TL, Rao PN, Surekha T, Ellanti R, Abhishek TL, Nath I.

- Clinical examination of enlarged nerves in leprosy patients is subjective and inaccurate
- Sonography provides an objective measure of nerve damage by showing increased vascularity, distorted echotexture and enlargement.
- This damage is sonographically more extensive and includes more nerves than clinically expected.



PLoS Negl Trop Dis. 2017 Jul 28;11(7):e0005766. doi: 10.1371/journal.pntd.0005766. eCollection 2017 Jul.

Extensive sonographic ulnar nerve enlargement above the medial epicondyle is a characteristic sign in Hansen's neuropathy.

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Author information

Abstract

OBJECTIVE: Earlier studies have shown sonographic enlargement of the ulnar nerve in patients with Hansen's neuropathy. The present study was performed to determine whether sonography or electrophysiological studies can detect the specific site of ulnar nerve pathology in leprosy.

METHODS: Eighteen patients (thirty arms) with Hansen's disease and an ulnar neuropathy of whom 66% had borderline tuberculoid (BT), 27% lepromatous leprosy (LL) and 7% mid-borderline (BB) leprosy were included in the study. Cross-sectional area (CSA) of ulnar nerve was measured every two centimeters from wrist to medial epicondyle and from there to axilla. All patients underwent standard motor and sensory nerve conduction studies of the ulnar nerve. Thirty age and sex matched controls underwent similar ulnar nerve CSA measurements and conduction studies.

RESULTS: Ulnar nerve was clinically palpable in 19 of the 30 arms of patients. Motor and sensory nerve conduction studies of the ulnar nerve showed a reduced compound motor action potential and sensory nerve action potential amplitude in all patients. Motor Conduction Velocity (MCV) in patients were slower in comparison to controls, especially at the elbow and upper arm, but unable to exactly locate the site of the lesion. In comparison to controls the ulnar nerveCSA was larger in the whole arm in patients and quite specific the maximum enlargement was seen between nulnar sulcus and axilla, peaking at four centimeters above the sulcus.

CONCLUSIONS: A unique sonographic pattern of nerve enlargement is noted in patients with ulnar neuropathy due to Hansen's disease, while this was not the case for the technique used until now, the electrodiagnostic testing. The enlargement starts at ulnar sulcus and is maximum four centimeters above the medial epicondyle and starts reducing further along the tract. This characteristic finding can help especially in diagnosing pure neuritic type of Hansen's disease, in which skin lesions are absent, and alsoto differentiate leprosy from other neuropathies in which nerve enlargement can occur.

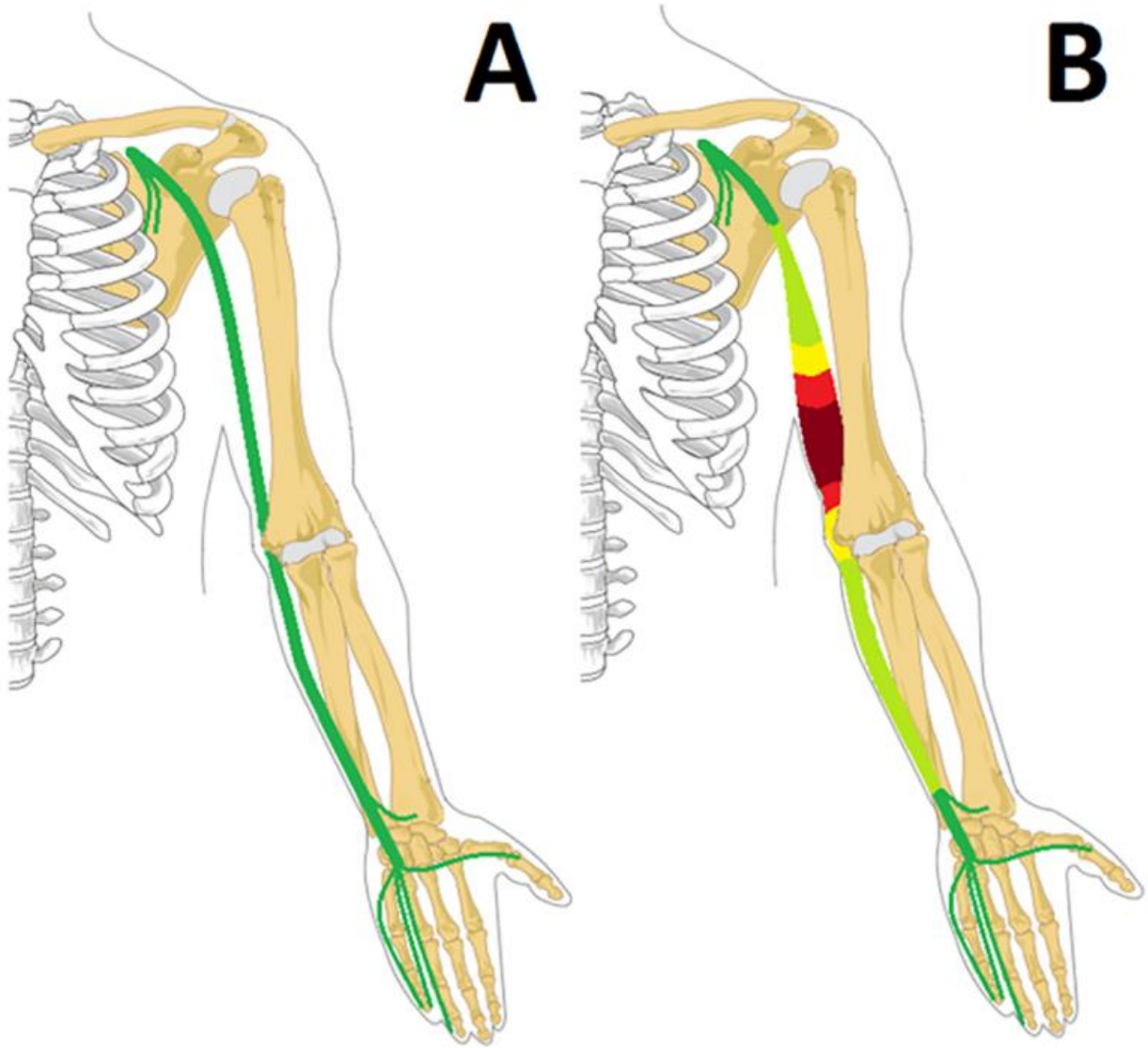
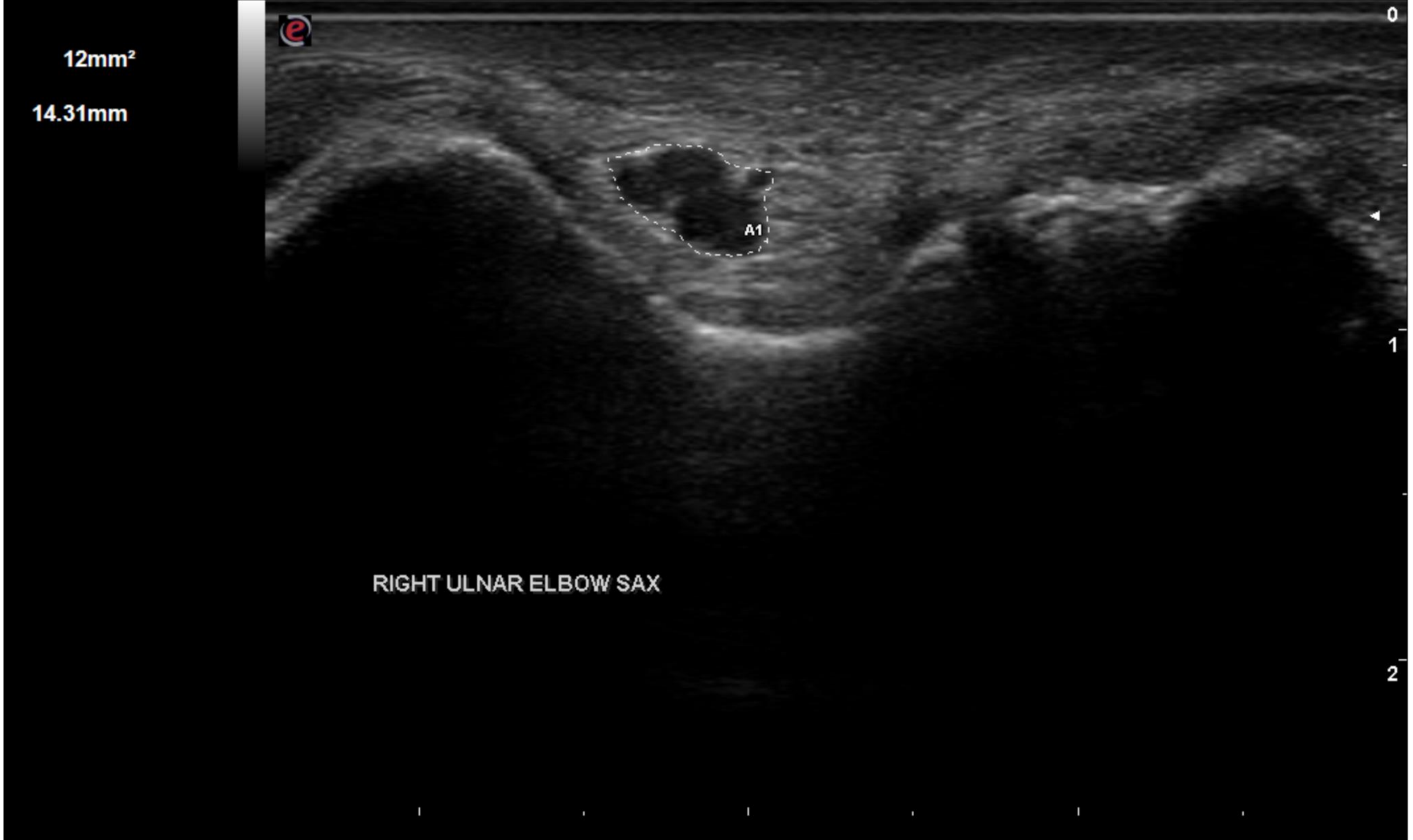
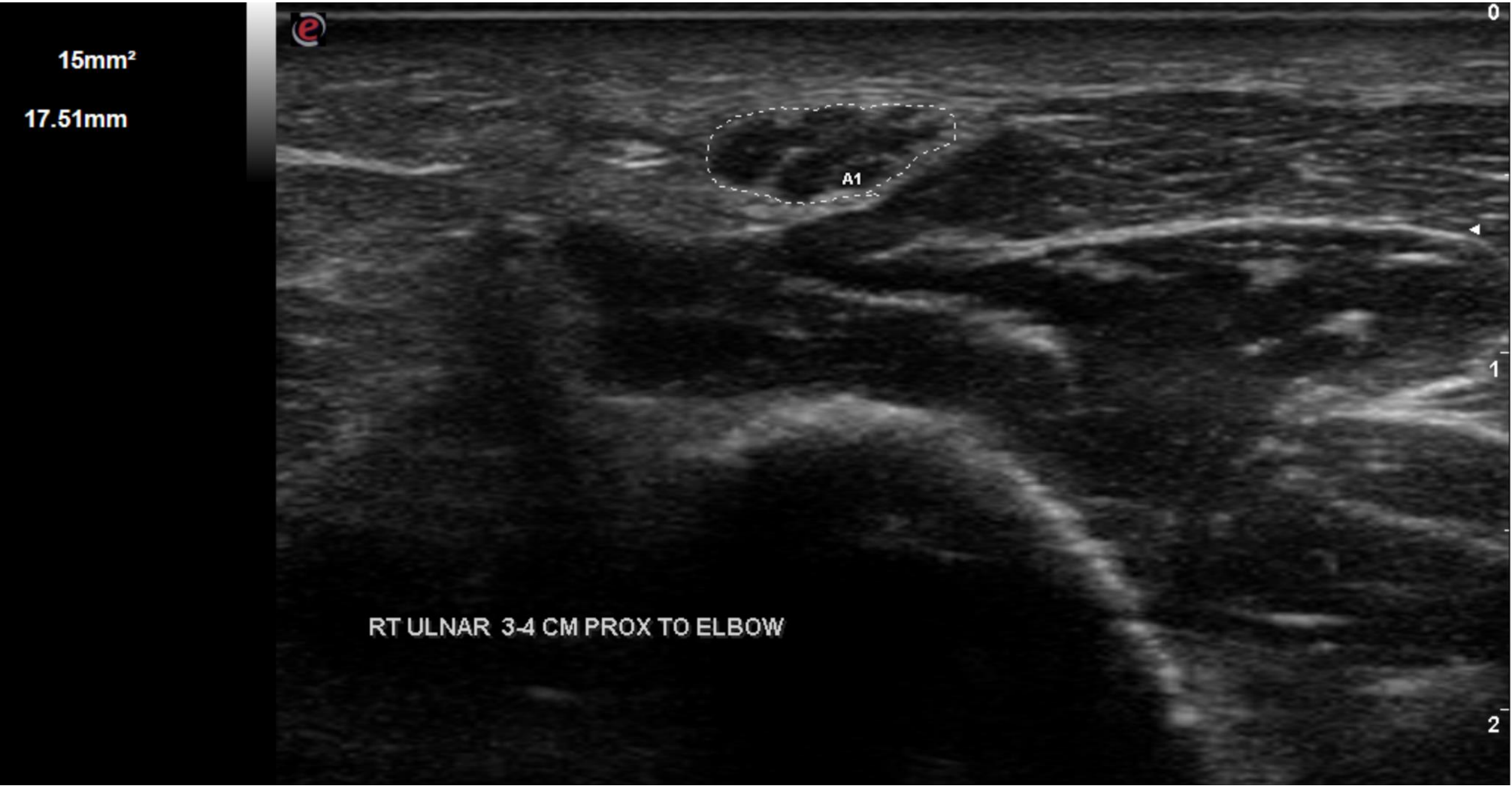


Fig 4. Pattern of nerve enlargement in leprosy. A—Normal ulnar nerve. B—Maximum enlargement few centimetres proximal to sulcus.

Bathala et al. PLOS
July 2017


12mm²
14.31mm
A1
RIGHT ULNAR ELBOW SAX
0
1
2


15mm²
17.51mm
A1
RT ULNAR 3-4 CM PROX TO ELBOW
0
1
2

1. R Median wrist - 18 mm2 (H-high), hypoechoic
2. R Median 2 cm prox to wrist - 14 mm2 (H), no increased vascularity
3. R Median mid forearm - 9 mm2 (borderline)
4. R Median elbow - 15 mm2 (H)
5. R Ulnar wrist - 9 mm2 (H), hypoechoic
6. R Ulnar distal forearm - 8 mm2 (upper normal)
7. R Ulnar elbow (cubital tunnel) - 12 mm2 (H), hypoechoic
8. R Ulnar 3-4 cm prox to elbow - 15 mm2 (H), hypoechoic, some increased vascularity
9. R Ulnar prox arm - 9 mm2 (borderline)
10. R tibial ankle - 19 mm2 (H), hypoechoic, no increased vascularity
11. R tibial prox ankle - 28 mm2 (H)
12. R Fibular n. at FH - 21 mm2 (H)
13. R Fibular n politeal fossa - 21 mm2 (H), hypoechoic, no increased vascularity
14. L Median wrist - 17 mm2 (H), hypoechoic
15. L Median 2 cm prox to wrist - 21 mm2 (H), hypoechoic, with increased vascularity
16. L Median mid forearm- 8 mm2 (normal)
17. L Ulnar elbow (cubital tunnel) - 11 mm2 (H), hypoechoic
18. L Ulnar 3-4 cm prox to elbow - 15 mm2 (H), hypoechoic, with increased vascularity
19. L tibial ankle - 25 mm2 (H), hypoechoic, no increased vascularity
20. L Fibular n at FH - 20 mm2 (H)
21. L Fibular n popliteal fossa - 22 mm2 (H), hypoechoic, no increased vascularity

Neuromuscular ultrasound evaluation of multiple nerves in all four extremities reveals diffuse and nonuniform enlargement of most nerves. Some nerves are hypoechoic and some have increased vascularity.

Chronic demyelinating polyneuropathies:

- **Inherited**
- **Acquired**

- **Immune-mediated** chronic demyelinating polyneuropathies
- **Nonimmune** chronic demyelinating polyneuropathies

- **CIDP** (Chronic inflammatory demyelinating polyradiculoneuropathy) is caused by acquired, immune-mediated demyelination of the nerves.

CIDP:

- In 1958 Austin et al. in Brain described a group of corticosteroid responsive recurrent polyneuropathies
- They used the term “polyradiculoneuropathy”
- In 1975 Dyck PJ et al. in Mayo Clinic Proc. described 53 patients with “chronic inflammatory polyradiculoneuropathy or CIP”
- They described the diagnostic criteria, natural history, nerve conduction characteristics, pathology, laboratory features, and efficacy of corticosteroid treatment for 53 patients who were followed up for an average of about 7.5 years.
- In 1982 Dyck PJ et al. designated the disorder as “chronic inflammatory-demyelinating polyneuropathy (CIDP)”

CIDP – chronic inflammatory demyelinating polyradiculoneuropathy:

- Affects 1.0 to 8.9 persons per 100,000
- Can occur at any age, but most commonly between 40 and 60 years
- Onset during infancy and childhood has been repeatedly documented
- It is a syndrome with **typical** and **atypical** variants
- It is caused by **cellular** and **humoral** immunologic dysfunction

Diagnostic Criteria for CIDP:

- There is no single reliable biomarker for CIDP
- More than 15 sets of CIDP diagnostic criteria are available, including Albers and Kelly (1985); Barohn et al (1989); Ad hoc subcommittee of the AAN (1991, research criteria); Bromberg et al (1991); Saperstein et al. (2001); Koski et al. (2009).
- Most commonly used are consensus derived the European Federation of Neurological Societies/ Peripheral Nerve Society **(EFNS/PNS)** criteria published in Journal of the Peripheral Nervous System in 2010
- The EFNS/PNS criteria have favorable sensitivity and specificity compared with other criteria:
  - Sensitivity: Definite 73.2%, Probable 76.8%, Possible 91.1%
  - Specificity: Definite 88.2%, Probable 84.2%, Possible 65.8 %

Diagnostic EFNS/PNS criteria for CIDP:

- Typical CIDP is a diagnosis that should be made based on **clinical** presentation and **electrodiagnostic evidence** (mandatory)
- Supportive evidence include lab evaluation, CSF, MRI, and nerve biopsy
- Recognizes many atypical forms of CIDP with slightly different clinical presentation

Typical CIDP:

- Patients present with relatively **SYMMETRIC PROXIMAL AND DISTAL weakness** and sensory dysfunction (**numbness**)
- Although pain and fatigue can occur, they should never be the defining clinical feature without motor and sensory deficits
- The disease course is steadily or stepwise progressive **over at least 2 months**, but can also be relapsing
- Up to **16%** of patients have an acute GBS-like presentation (**Acute CIDP variant** with progression less than 2 months)
- In contrast with GBS, cranial nerves are rarely affected; respiratory or autonomic involvement is exceptional and there is no preceding infectious illness.
- Neurological examination shows **reduced or absent** muscle stretch reflexes
- Electrophysiology shows generalized demyelinating features

Atypical CIDP	DADS	Predominantly distal sensory more than motor	Deep tendon reflexes reduced or absent distally, may be normal or reduced in proximal areas	Distally accentuated demyelination
	MADSAM (Lewis-Sumner syndrome)	Asymmetric motor and sensory	Deep tendon reflexes may be normal in unaffected limb	Multifocal demyelination; motor and sensory
	Motor CIDP	Proximal and distal motor	Deep tendon reflexes generally reduced	Generalized motor demyelination; sensory spared
	Sensory CIDP; CISP	Proximal and distal sensory	Absent or reduced deep tendon reflexes in all limbs	Normal or small sensory responses; prolonged somatosensory evoked potentials; motor spared

DADS no MAG variant- Distal acquired demyelinating symmetric neuropathy without myelin-associated glycoprotein); MADSAM – Multifocal acquired demyelinating sensory and motor neuropathy

(from Neurology Continuum October 2017)

DADS:

Distal acquired demyelinating symmetric neuropathy

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Article abstract—*Objective:* To characterize an acquired, symmetric, demyelinating neuropathic variant with distal sensory or sensorimotor features. *Background:* Classic chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) patients have prominent proximal and distal weakness. However, chronic demyelinating neuropathies may present with different phenotypes. An approach that distinguishes these disorders primarily according to the pattern of weakness may be useful to the clinician. *Methods:* A total of 53 patients with acquired symmetric demyelinating polyneuropathies were classified primarily according to the pattern of the neuropathy and secondarily according to the presence and type of monoclonal protein (M-protein) in this retrospective review. The authors distinguished between patients with distal sensory or sensorimotor involvement, designated as distal acquired demyelinating symmetric (DADS) neuropathy, from those with proximal and distal weakness, who were designated as CIDP. *Results:* M-proteins were present in 22% of patients with CIDP. There were no features that distinguished clearly between CIDP patients with or without an M-protein, and nearly all of these patients responded to immunomodulating therapy. In contrast, nearly two-thirds of the patients with DADS neuropathy had immunoglobulin M (IgM) kappa monoclonal gammopathies, and this specific combination predicted a poor response to immunomodulating therapy. Antimyelin-associated glycoprotein (anti-MAG) antibodies were present in 67% of these patients. *Conclusion:* Distinguishing acquired demyelinating neuropathies by phenotype can often predict the presence of IgM kappa M-proteins, anti-MAG antibodies, and responses to immunomodulating therapy.
Key words: Chronic inflammatory demyelinating polyradiculopathy—Distal acquired demyelinating symmetric neuropathy—Monoclonal gammopathy of uncertain significance—Terminal latency index—Myelin-associated glycoprotein.

NEUROLOGY 2000;54:615–620

DADS no MAG (without IgM Paraprotein)

- DADS without a paraprotein (no MAG) represents an atypical form of CIDP (distal presentation of CIDP)
- Defined as distal sensory neuropathy
- Clinical features: sensory loss plus ankle dorsiflexion and intrinsic foot muscle weakness with areflexia
- EDX: evidence of demyelination affecting motor as well as sensory nerve fibers
- Majority: CSF with high protein
- Key difference with CIDP is in the differential diagnosis, not in the treatment
- Key differential diagnosis is other length-dependent polyneuropathies (idiopathic and diabetic most common)
- Once diagnosed: Response to first-line treatment is similar to the response of typical CIDP

DADS with IgM Paraprotein (anti-MAG):

- This appears to be a distinct disorder
- Older age
- Mostly men
- IgM paraprotein
- Usually kappa light chains
- Autoantibodies to MAG in many of these cases
- Distal slowing on NCS
- Respond poorly to immune therapies

Diagnostic EFNS/PNS criteria for CIDP:

1. Clinical: typical and atypical CIDP
2. Electrodiagnostic: definite, probable and possible CIDP
3. Supportive; including CSF, MRI, nerve biopsy and treatment response
4. Categories: definite, probable, and possible CIDP

(Joint Task Force of the EFNS and the PNS,

Journal of the Peripheral Nervous System 15:1-9 (2010)

European Journal of Neurology 2010, 17: 356–363)

Diagnostic EFNS/PNS criteria for CIDP:

Table 4 Clinical diagnostic criteria

(1) Inclusion criteria
- (a) Typical CIDP
  - Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and
  - Absent or reduced tendon reflexes in all extremities
- (b) Atypical CIDP (still considered CIDP but with different features)
  - One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):
  - Predominantly distal (distal acquired demyelinating symmetric, DADS) or
  - Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis–Sumner syndrome] or
  - Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)
  - Pure motor or
  - Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)

(2) Exclusion criteria
- Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy
- Hereditary demyelinating neuropathy
- Prominent sphincter disturbance
- Diagnosis of multifocal motor neuropathy
- IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein
- Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features

Diagnostic EFNS/PNS criteria for CIDP:

Table 1 Electrodiagnostic criteria

(1) Definite: at least one of the following
  (a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
  (b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or
  (c) Prolongation of F-wave latency ≥30% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP < 80% of LLN values), or
  (d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or
  (e) Partial motor conduction block: ≥50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or
  (f) Abnormal temporal dispersion (> 30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves, or
  (g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms)[b] + ≥1 other demyelinating parameter[a] in ≥1 other nerve
(2) Probable
  ≥30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter[a] in ≥1 other nerve
(3) Possible
  As in (1) but in only one nerve

To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. If criteria are not fulfilled, the same nerves are tested at the other side, and/or the ulnar and median nerves are stimulated bilaterally at the axilla and at Erb's point. Motor conduction block is not considered in the ulnar nerve across the elbow and at least 50% amplitude reduction between Erb's point and the wrist is required for probable conduction block. Temperatures should be maintained to at least 33°C at the palm and 30°C at the external malleolus (good practice points).

CMAP, compound muscle action potential; ULN, upper limit of normal values; LLN, lower limit of normal values.

[a]Any nerve meeting any of the criteria (a–g).

[b]Isose S. *et al.*, in press [16].

Needle EMG:

- Routine needle EMG is less important than nerve conduction studies
- Documents axonal loss, but cannot distinguish primary vs secondary axonal loss

Diagnostic EFNS/PNS criteria for CIDP:

Table 5 Supportive criteria

1. Elevated CSF protein with leukocyte count $< 10/mm^3$ (level A recommendation)
2. MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses (level C recommendation)
3. Abnormal sensory electrophysiology in at least one nerve (good practice points):
   a. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or
   b. Conduction velocity $< 80\%$ of lower limit of normal ($< 70\%$ if SNAP amplitude $< 80\%$ of lower limit of normal); or
   c. Delayed somatosensory evoked potentials without central nervous system disease
4. Objective clinical improvement following immunomodulatory treatment (level A recommendation)
5. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis (good practice point)

Diagnostic EFNS/PNS criteria for CIDP:

Table 6 Diagnostic categories

Definite CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 1; or
Probable CIDP + at least one supportive criterion; or
Possible CIDP + at least two supportive criteria
Probable CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 2; or
Possible CIDP + at least one supportive criterion
Possible CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 3
CIDP (definite, probable, possible) associated with concomitant diseases.

Exclusionary Neuropathies:

Exclusionary Conditions	Investigation in Appropriate Clinical Setting
Multifocal motor neuropathy (MMN)	Anti-GM1 antibody
Anti–myelin-associated glycoprotein (MAG)	Serum/urine immunofixation, anti-MAG antibody, skeletal survey
Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome	Serum/urine immunofixation, vascular endothelial growth factor, skeletal survey
Sarcoidosis	Chest and abdominal imaging, nerve biopsy
Lyme	*Borrelia burgdorferi* serology, CSF (pleocytosis)
Diphtheria	Clinical suspicion, *Corynebacterium diphtheriae* by culture
Amyloidosis	Serum/urine immunofixation, *TTR* genetic testing, nerve or fat-pad biopsy
Hereditary	Appropriate genetic testing
Peripheral nervous system lymphoma	Chest and abdominal imaging, nerve biopsy
Toxic/iatrogenic	Thorough medication exposure history
Myelopathy	Thorough examination for upper motor neuron findings, MRI spinal cord

Diagnostic EFNS/PNS criteria for CIDP:

Table 2 Investigations to be considered

To diagnose chronic inflammatory demyelinating polyradiculoneuropathy
Electrodiagnostic studies including sensory and motor nerve conduction studies, which may be repeated, performed bilaterally, or use proximal stimulation for motor nerves
CSF examination including cells and protein
MRI spinal roots, brachial plexus, and lumbosacral plexus
Nerve biopsy
To detect concomitant diseases
(a) Recommended studies
[a]Serum and urine paraprotein detection by immunofixation
Fasting blood glucose
Complete blood count
Renal function
Liver function
Antinuclear factor
Thyroid function
(b) Studies to be performed if clinically indicated
[a]Skeletal survey
Oral glucose tolerance test
Borrelia burgdorferi serology
C reactive protein
Extractable nuclear antigen antibodies
Chest radiograph
Angiotensin-converting enzyme
HIV antibody
To detect hereditary neuropathy
Examination of parents and siblings
Appropriate gene testing (especially PMP22 duplication and connexin 32 mutations)
Nerve biopsy

[a]Repeating these should be considered in patients who are or become unresponsive to treatment.

CIDP – Treatment (EFNS/PNS recommendations):

- IVIG (level A recommendation) or corticosteroids (level C recommendation) should be considered in sensory and motor CIDP in the presence of disabling symptoms
- IVIG should be considered as the initial treatment in pure motor CIDP (good practice point)
- If IVIG and corticosteroids are ineffective, plasma exchange should be considered (level A recommendation)
- The presence of relative contraindications to any of these treatments should influence the choice
- The advantages and disadvantages should be explained to the patient who should be involved in the decision making

CIDP – Treatment (EFNS/PNS recommendations):

- If the first-line treatment is effective, continuation should be considered until the maxium benefit has been achieved and then the dose reduced to find the lowest effective maintenance dose
- If the response is inadequate or the maintenance doses of the initial treatment (IVIG, steroids, or PE) result in adverse effects, the other first-line treatment alternatives should be tried before considering combination treatments or adding an immuno-suppressant or immunomodulatory drug may be considered, but there is no sufficient evidence to recommend any particular drug

Misdiagnosis of CIDP:

CIDP diagnostic pitfalls and perception of treatment benefit

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ABSTRACT

Objective: We aimed to explore the diagnosis and misdiagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) and to identify pitfalls that erroneously lead to a misdiagnosis.

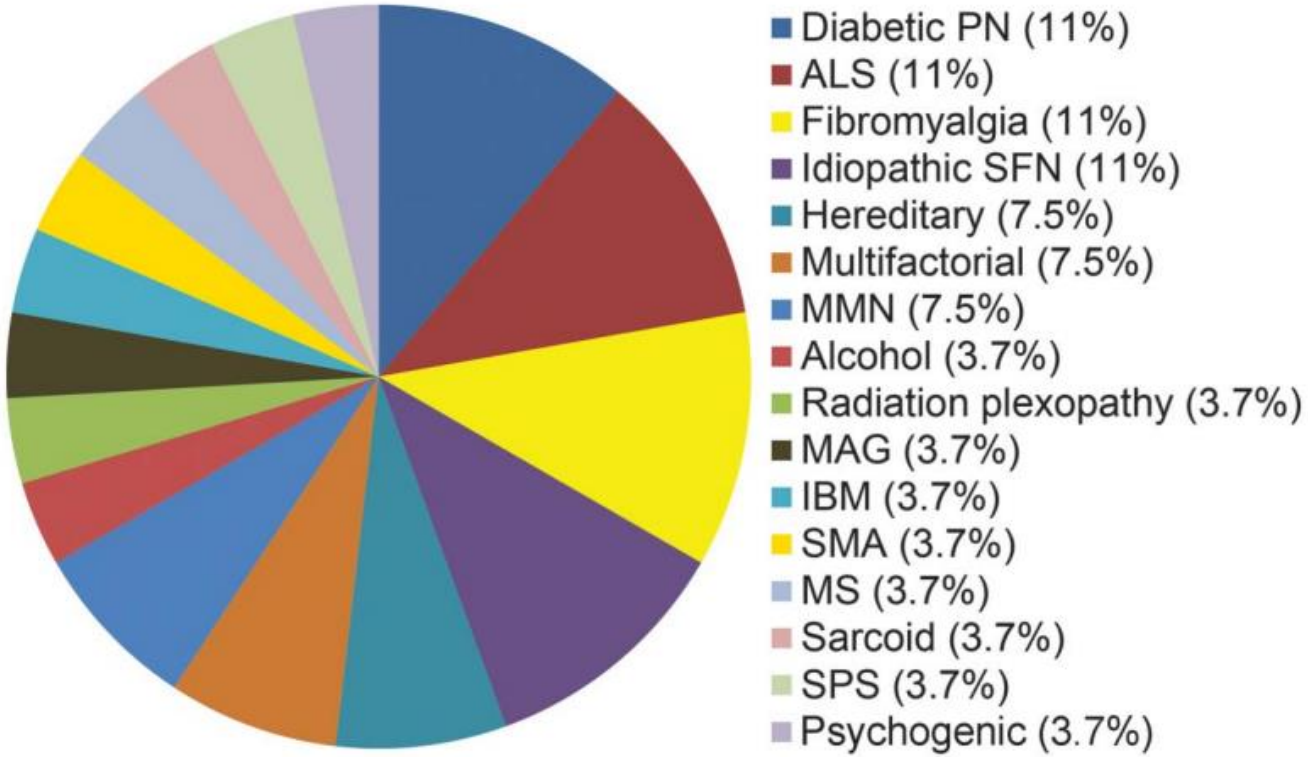
Methods: A retrospective study of 59 consecutive patients referred with a diagnosis of CIDP was performed. Patients were classified as having or not having CIDP according to European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria. Diagnostic and treatment data were compared in the 2 groups.

Results: Forty-seven percent of patients referred with a diagnosis of CIDP failed to meet minimal CIDP diagnostic requirements. All misdiagnosed patients who satisfied EFNS/PNS clinical criteria would be considered atypical as defined by the EFNS/PNS. CSF cytoalbuminologic dissociation was present in 50% of those without CIDP, although protein elevations were generally mild. Nerve conduction studies in patients without CIDP were heterogeneous, but generally showed demyelinating features better explained by a process other than CIDP. Patients frequently reported improvements after being treated with immunotherapy, even if the CIDP diagnosis was incorrect.

Conclusions: CIDP misdiagnosis is common. Over-reliance on subjective patient-reported perception of treatment benefit, liberal electrophysiologic interpretation of demyelination, and placing an overstated importance on mild or moderate cytoalbuminologic dissociation are common diagnostic errors. Utilization of clear and objective indicators of treatment efficacy might improve our ability to make informed treatment decisions. ***Neurology*® 2015;85:498–504**

Misdiagnosis of CIDP:

Figure **Alternative diagnosis for patients without chronic inflammatory demyelinating polyneuropathy**



ALS = amyotrophic lateral sclerosis; IBM = inclusion body myositis; MAG = myelin-associated glycoprotein; MMN = multifocal motor neuropathy; MS = multiple sclerosis; PN = polyneuropathy; SFN = small fiber neuropathy; SMA = spinal muscular atrophy; SPS = stiff person syndrome.

Diagnostic data for patients with and without CIDP:

EFNS/PNS clinical criteria, %	100	44	<0.01
EFNS/PNS clinical criteria, typical, %	80.6	0	<0.01
EFNS/PNS electrodiagnostic criteria, %	100	14.8	<0.01
EFNS/PNS electrodiagnostic criteria, definite, %	84.4	11.1	<0.01
CSF cytoalbuminologic dissociation, % (n)	90.3 (31)	50.0 (20)	0.02
CSF protein mg/dL, mean (SD, range)	156.3 (130.5, 33-550)	61.4 (30.7, 18-128)	<0.01
MRI nerve root enhancement/enlargement, % (n)	75 (24)	10.5 (19)	<0.01
Nerve biopsy demyelination/remyelination, % (n)	50 (6)	0 (7)	<0.01

Misdiagnosis of CIDP:

ELECTRODIAGNOSTIC ERRORS CONTRIBUTE TO CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY MISDIAGNOSIS

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Accepted 13 October 2017

ABSTRACT: *Introduction:* Documentation of peripheral nerve demyelination is an important part of the **c**hronic inflammatory demyelinating polyneuropathy (CIDP) diagnostic process.

Methods: We performed a retrospective analysis of patients referred with a diagnosis of CIDP who were found to have a different condition. Electrodiagnostic study data and interpretations formulated at the time of the initial diagnosis were compared to those obtained during the reevaluation.

Results: Thirty-nine of 86 patients were found not to have CIDP. Initial electrodiagnostic data quality was generally acceptable, but initial electrodiagnostic conclusions were confirmed in only 45% of misdiagnosed studies.

Discussion: Vulnerability to interpretive errors increases when amplitude-dependent slowing occurs with length-dependent axonal neuropathies or motor neuron disease, amplitude-independent slowing occurs in diabetic patients, fibular nerve to extensor digitorum brevis (EDB) muscle findings are the focal diagnostic abnormality, conduction block is absent, conduction velocity (CV) slowing is limited to compressible sites, and accurate electrodiagnostic interpretations are dismissed in favor of equivocal clinical and cerebrospinal fluid findings.

Muscle Nerve **000**:000–000, 2017

unknown. Regardless of the specific criteria used, or even if no diagnostic guideline is referenced, one critical aspect of CIDP diagnosis is documentation of peripheral nerve demyelination on nerve conduction studies (NCS).

The diagnosis of CIDP is made by carefully integrating demyelinating electrophysiological findings with key clinical features and laboratory abnormalities. In a disease such as CIDP, in which there is no single reliable biomarker, critical assessment of each component is important. Just as with most diagnostic guidelines, the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria[7] are consensus derived. Developed to be inclusive of typical and atypical CIDP variants, the EFNS/PNS criteria have favorable sensitivity and specificity compared with other criteria.[6] A diagnosis of CIDP can reliably be

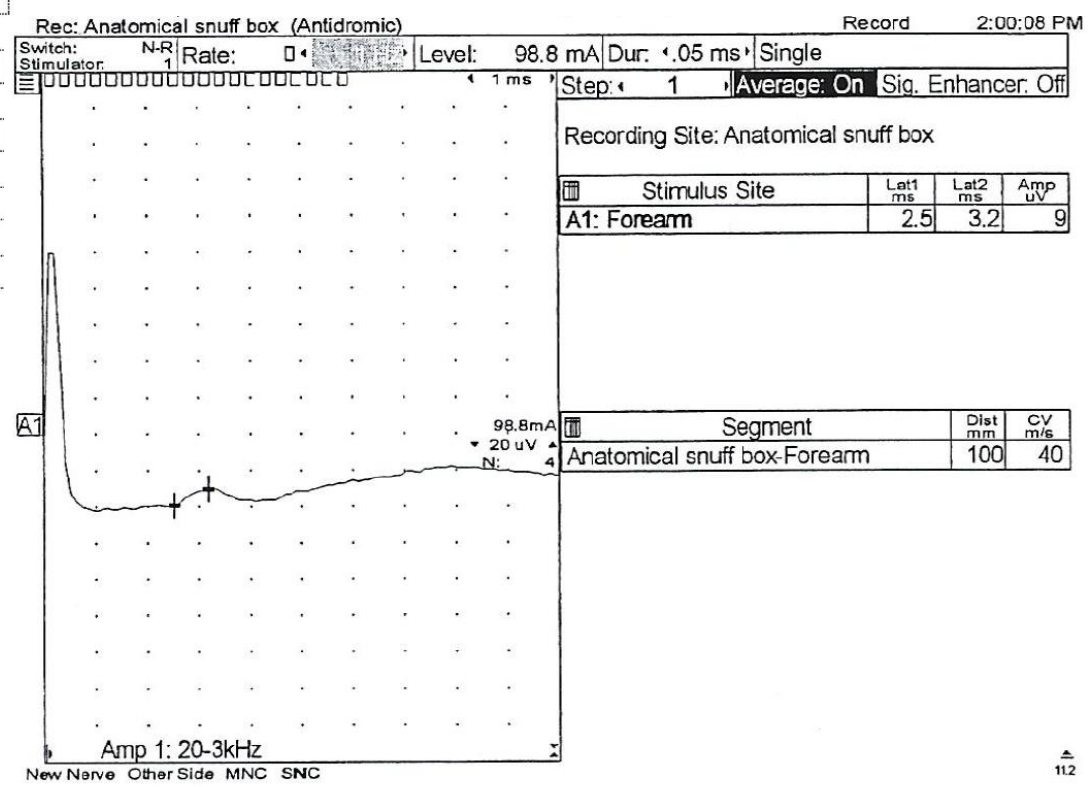
Case #2: Increased leg pain + abnormal gait:

- M in early 50ties presents with worsening of RLE pain and increased difficulty walking.
- Long standing h/o HIV, on antiviral treatment (combination).
- Late 1990ties diagnosed by 3 universities with progressive multifocal leukoencephalopathy (PML) with right hemiparesis and ataxia.
- H/o abnormal CSF and abnormal brain MRI in 1990ties.
- Exam positive for bilateral hammertoes.

EMG/NCS (after adequate warming):

Sensory and Mixed Nerve Conduction:

Nerve and Site	Onset Lat ms	Peak Lat ms	Amp µV	Segment	Lat Diff ms	Dist mm	CV m/s
Sural.L to Ankle.L							
Lower leg	NR	NR	NR	Ankle-Lower leg		120	
Superficial peroneal.L to Ankle.L							
Lower leg	NR	NR	NR	Ankle-Lower leg		120	
Sural.R to Ankle.R							
Lower leg	NR	NR	NR	Ankle-Lower leg		120	
Superficial peroneal.R to Ankle.R							
Lower leg	NR	NR	NR	Ankle-Lower leg		120	
Median.R to Digit II (index finger).R							
Wrist	NR	NR	NR	Digit II (index finger)-Wrist		140	
Ulnar.R to Digit V (little finger).R							
Wrist	NR	NR	NR	Digit V (little finger)-Wrist		130	
Radial.R to Anatomical snuff box.R							
Forearm	2.5	3.2	9	Anatomical snuff box-Forearm	2.5	100	40



Motor Nerve Conduction:

Nerve and Site	Lat ms	Amp mV	Segment	Dist mm	Lat Diff ms	CV m/s
Peroneal.L to Extensor digitorum brevis.L						
Ankle	NR	NR	Extensor digitorum brevis-Ankle	80		
Fibula (head)	NR	NR	Ankle-Fibula (head)	325		
Peroneal.L to Tibialis anterior.L						
Fibula (head)	3.9	2.7	Tibialis anterior-Fibula (head)	90	3.9	
Popliteal fossa	6.7	2.5	Fibula (head)-Popliteal fossa	110	2.8	39
Tibial.L to Abductor hallucis.L						
Ankle	8.3	0.9	Abductor hallucis-Ankle	80	8.3	
Popliteal fossa	22.9	0.7	Ankle-Popliteal fossa	445	14.6	30
Peroneal.R to Extensor digitorum brevis.R						
Ankle	NR	NR	Extensor digitorum brevis-Ankle	80		
Fibula (head)	NR	NR	Ankle-Fibula (head)			
Tibial.R to Abductor hallucis.R						
Ankle	6.2	1.7	Abductor hallucis-Ankle	80	6.2	
Popliteal fossa	23.7	1.3	Ankle-Popliteal fossa	465	17.5	27
Peroneal.R to Tibialis anterior.R						
Fibula (head)	6.1	1.8	Tibialis anterior-Fibula (head)	120	6.1	
Popliteal fossa	10.8	1.3	Fibula (head)-Popliteal fossa	105	4.7	22
Median.R to Abductor pollicis brevis.R						
Wrist	7.5	9.1	Abductor pollicis brevis-Wrist	70	7.5	
Elbow	14.9	8.3	Wrist-Elbow	265	7.4	36
Ulnar.R to Abductor digiti minimi (manus).R						
Wrist	7.0	9.6	Abductor digiti minimi (manus)-Wrist	70	7.0	
Below elbow	13.5	8.0	Wrist-Below elbow	230	6.5	35
Above elbow	16.9	5.9	Below elbow-Above elbow	100	3.4	29

F-waves:

Nerve	M-Lat ms	F-Lat ms
Tibial.L	9.1	88.0
Tibial.R	6.4	78.7
Median.R	6.8	47.1
Ulnar.R	7.0	47.1

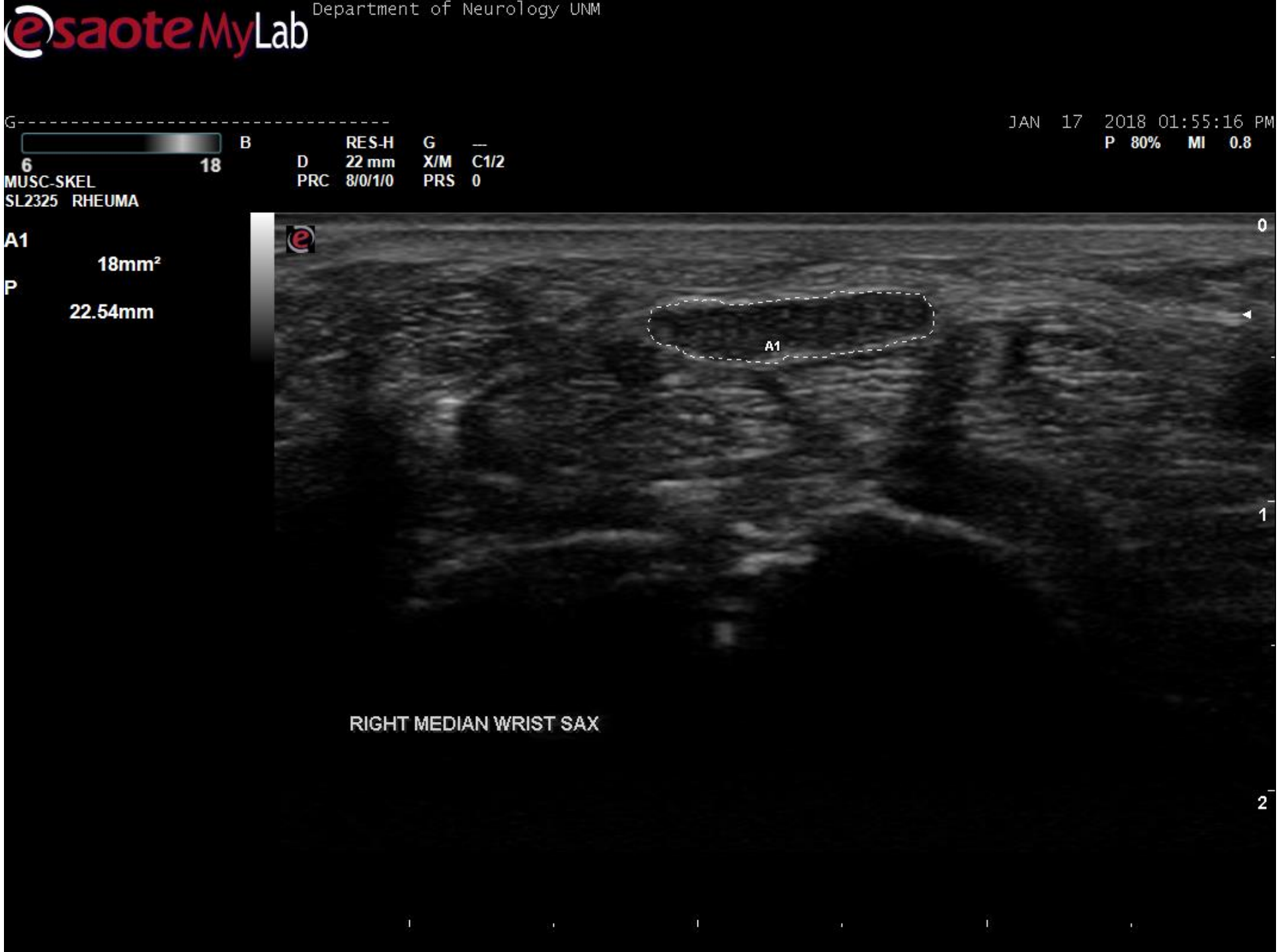
Needle EMG Examination:

Muscle	Insertion Activity	Spontaneous Activity				Volutional MUAPs					Comments
		Fibs	PSW	Fasc	Other	Effort	Recruit	Dur	Amp	Poly	
Deltoid.R	Normal	None	None	None		Normal	Normal	Normal	Normal	None	Tremulous
Triceps brachii.R	Normal	None	None	None		Normal	Normal	Normal	Normal	None	Tremulous
Biceps brachii.R	Normal	None	None	None		Normal	Normal	Normal	Normal	None	Tremulous
1st dorsal interosseous.R	Normal	None	None	None		Normal	Reduced	Sl. Incr.	Sl. Incr.	Rare	Tremulous
Extensor indicis proprius.R	Normal	None	None	None		Normal	Normal	Normal	Normal	None	Tremulous
Abductor pollicis brevis.R	Normal	None	None	None		Normal	Sl.reduced	Sl. Incr.	Sl. Incr.	Rare	Tremulous
Tibialis anterior.R	Normal	None	None	None		Normal	Sl.reduced	Sl. Incr.	Gr. Incr.	None	
Gastrocnemius (Medial head).R	Normal	None	None	None		Normal	Sl.reduced	Sl. Incr.	Sl. Incr.	None	
Vastus lateralis.R	Normal	None	None	None		Normal	Normal	Normal	Normal	None	
Tensor fasciae latae.R	Normal	None	None	None		Normal	Sl.reduced	Sl. Incr.	Sl. Incr.	None	
Lum Para Low .R	Normal	None	None	None							
Lum Para Low .L	Normal	None	None	None							
Tibialis anterior.L	Normal	None	None	None		Normal	Sl.reduced	Sl Incr	Gr Incr	None	
Gastrocnemius (Medial head).L	Normal	None	None	None		Normal	Sl.reduced	Sl. Incr.	Sl. Incr.	None	
Vastus lateralis.L	Normal	None	None	None		Normal	Normal	Normal	Normal	None	
Tensor fasciae latae.L	Normal	None	None	None		Normal	Normal	Normal	Normal	None	

Impression:

This is an abnormal study. Electrodiagnostic testing is mostly consistent with chronic sensorimotor polyneuropathy with both demyelinating and axonal features. Patient reportedly has not had any EMG/NCS studies in the past, but he has long standing h/o HIV and h/o progressive multifocal leukoencephalopathy (PML) with right sided hemiplegia/ataxia since late 1990ties.

Additionally, his electrodiagnostic testing today is suggestive of likely superimposed chronic, mild right L5 radiculopathy.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Department of Neurology UNM
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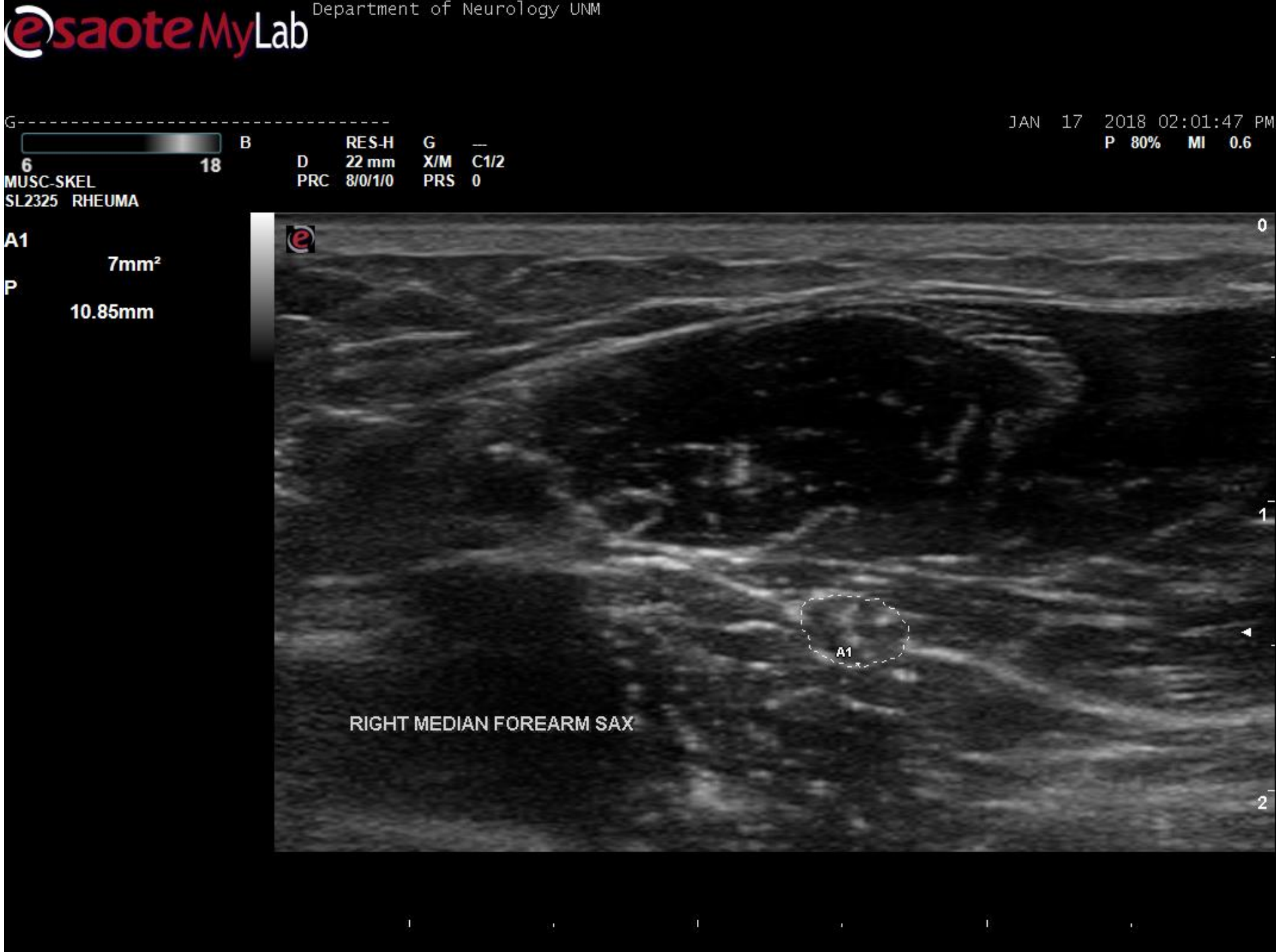
PRC 8/0/1/0 PRS 0
6 18
MUSC-SKEL
SL2325 RHEUMA
A1
18mm²
P
22.54mm
A1
0
1
2
RIGHT MEDIAN WRIST SAX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Department of Neurology UNM
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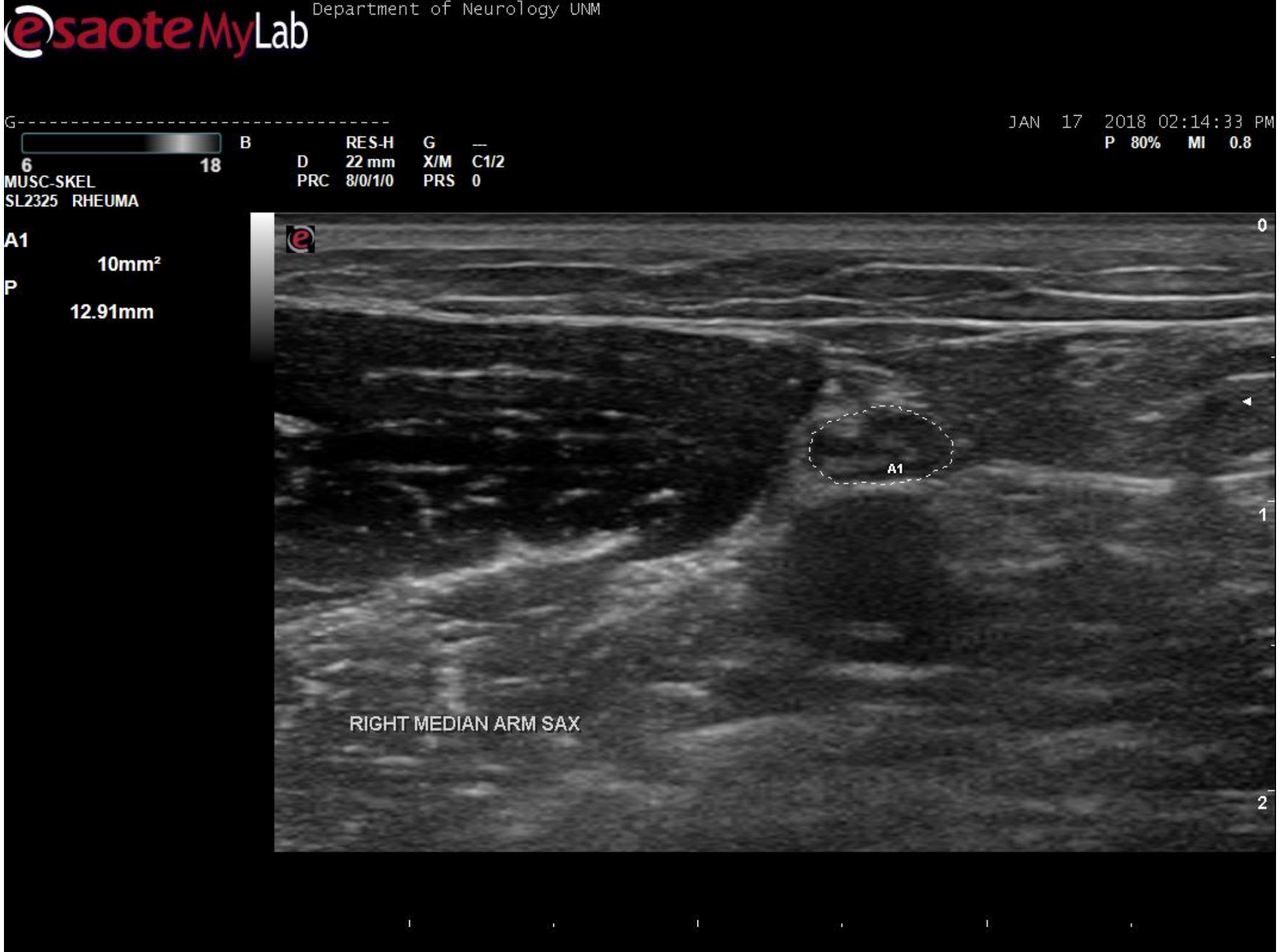
RIGHT MEDIAN FOREARM SAX
0
1
2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Department of Neurology UNM
G----------
B
RES-H
G
—
6
18
D
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X/M
C1/2
PRC
8/0/1/0
PRS
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A1
RIGHT MEDIAN ARM SAX
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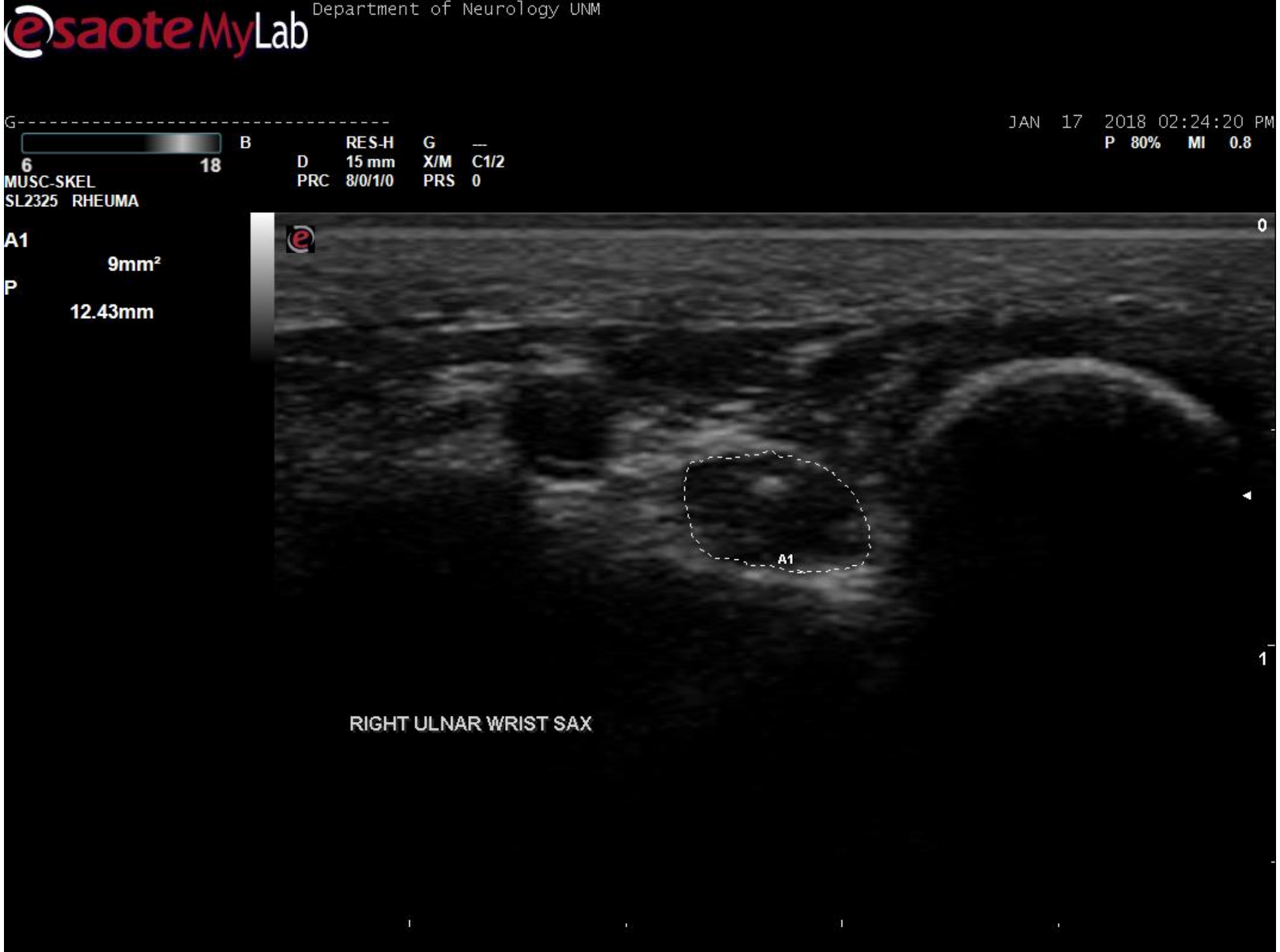
1
2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Department of Neurology UNM
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—
6
18
D
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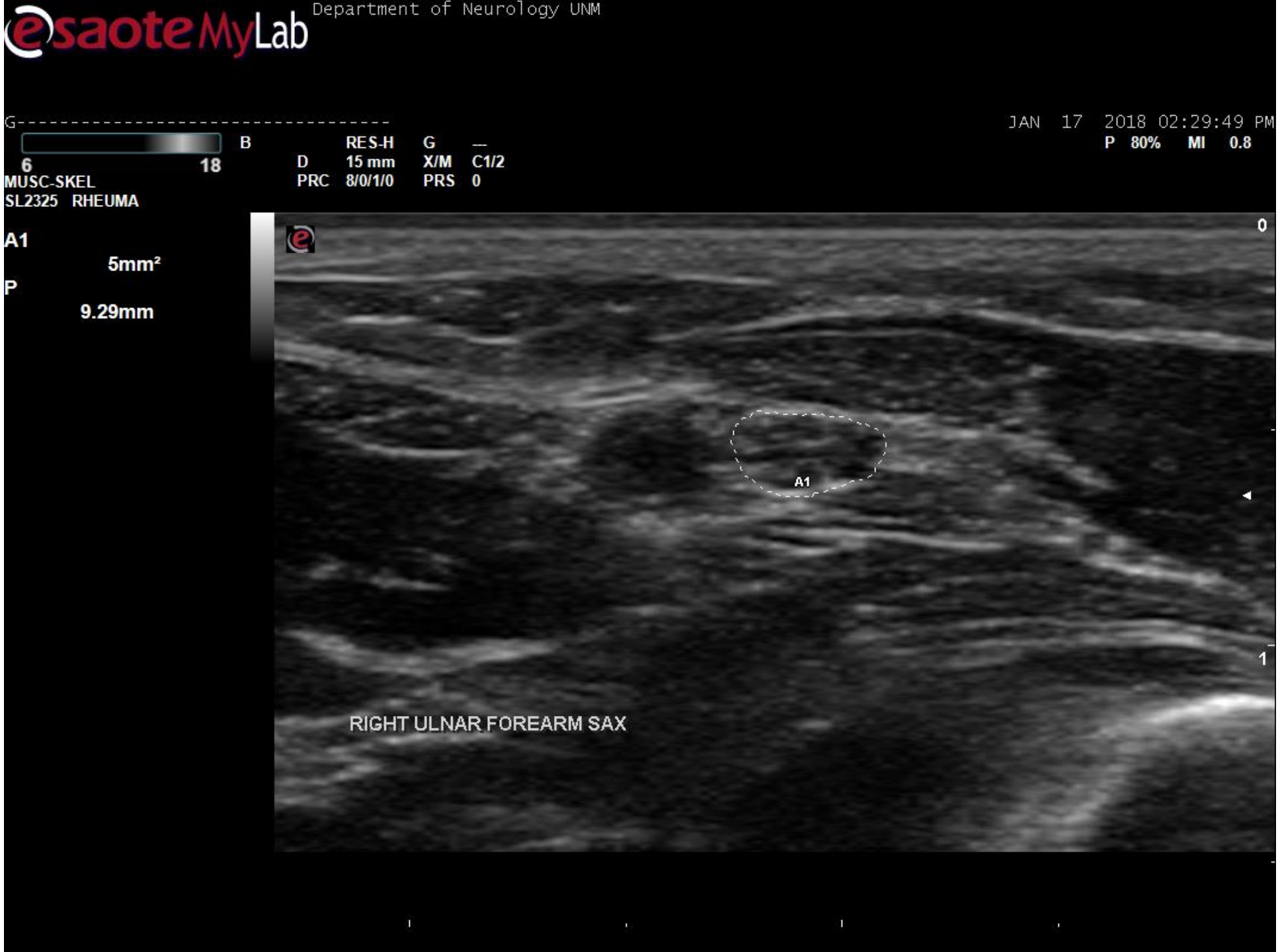
X/M
C1/2
P 80%
MI 0.8
PRC 8/0/1/0
PRS 0
MUSC-SKEL
SL2325 RHEUMA
A1
9mm²
P
12.43mm
0
A1
1
RIGHT ULNAR WRIST SAX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SL2325 RHEUMA
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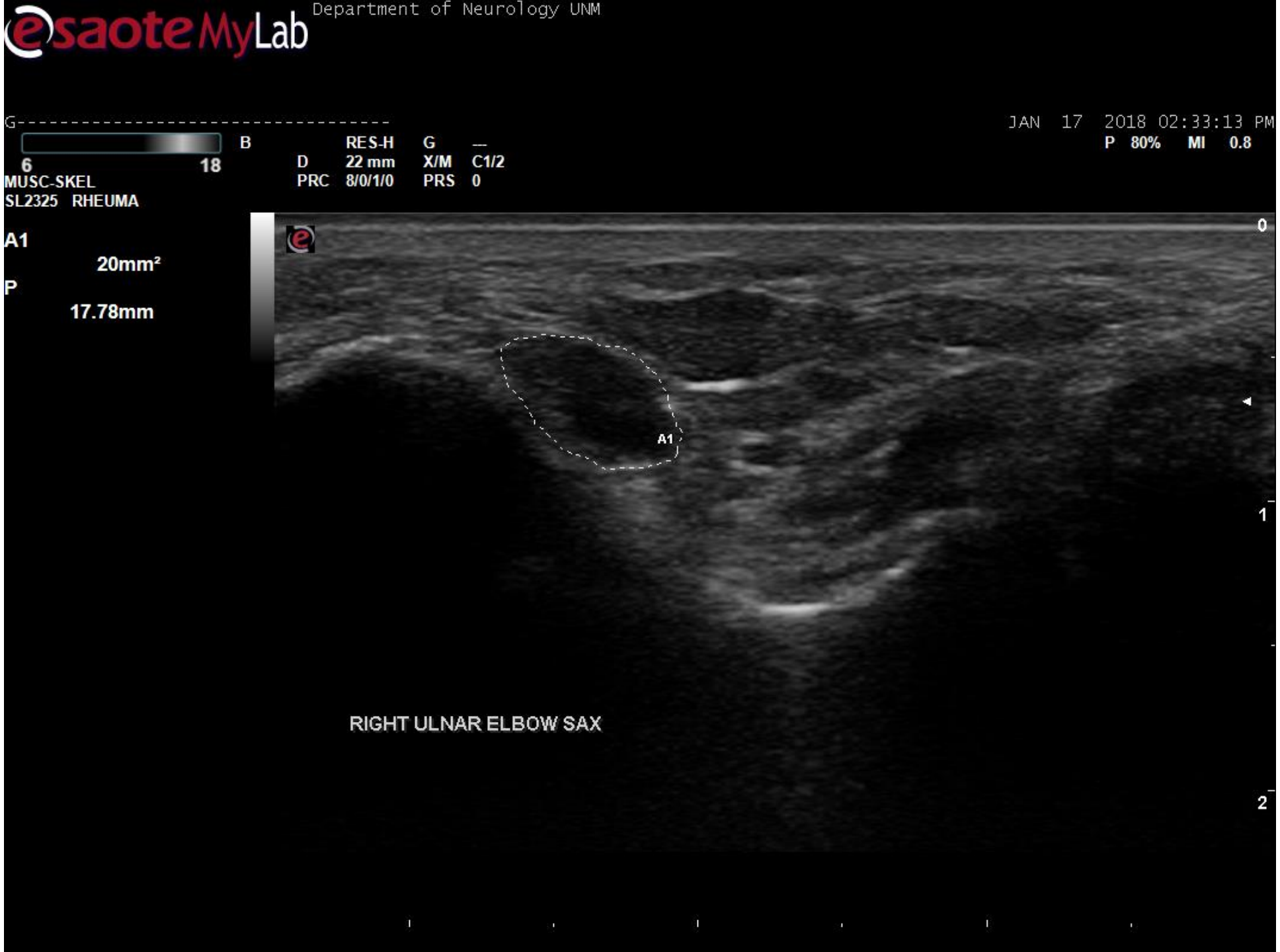
P
9.29mm
A1
0
1
RIGHT ULNAR FOREARM SAX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RES-H
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18
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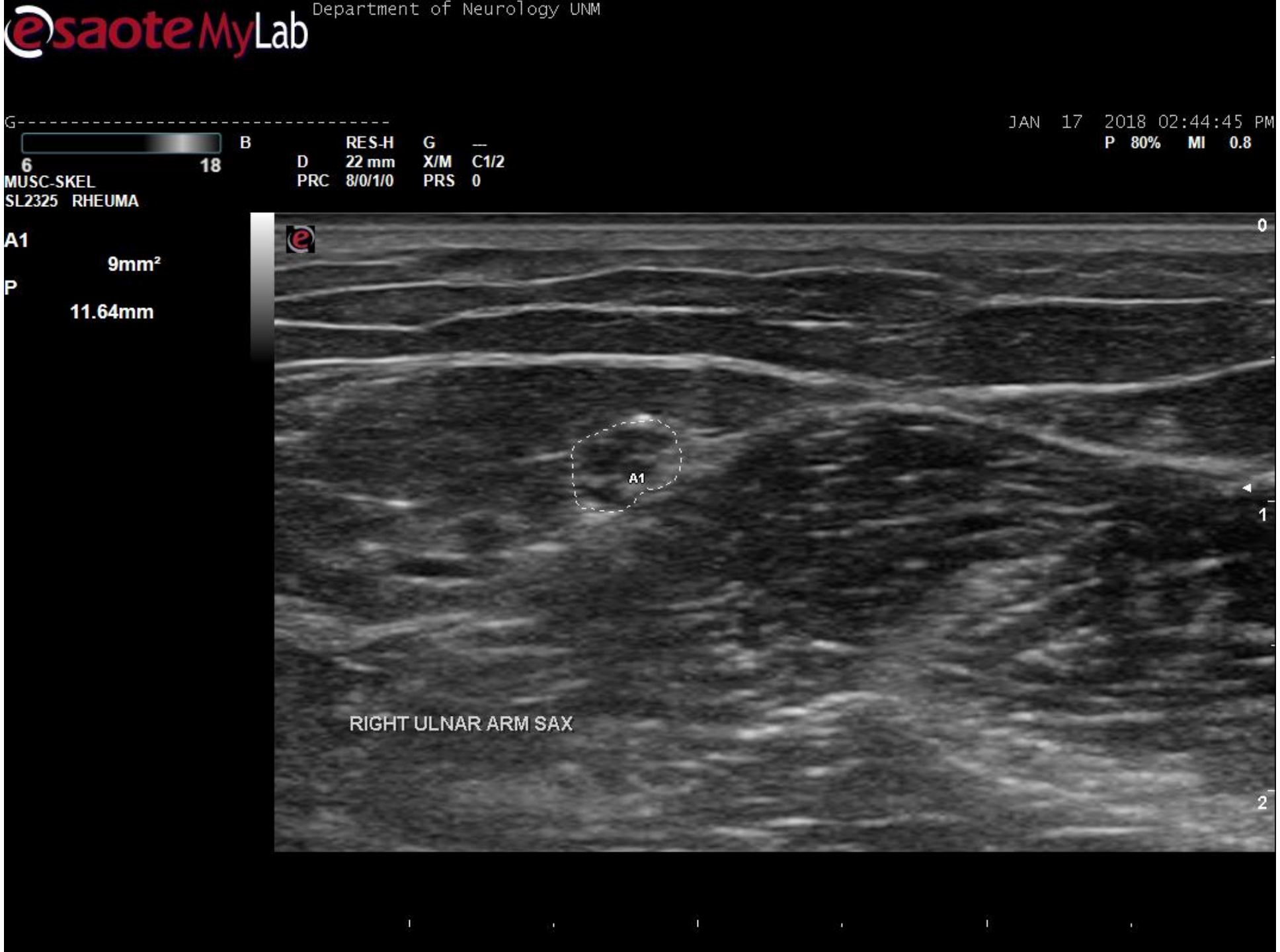
X/M
C1/2
P 80%
MI 0.8
PRC 8/0/1/0
PRS 0
MUSC-SKEL
SL2325 RHEUMA
A1
20mm²
P
17.78mm
A1
0
1
2
RIGHT ULNAR ELBOW SAX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Department of Neurology UNM
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G
6
18
D
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C1/2
P 80%
MI 0.8
PRC 8/0/1/0
PRS 0
MUSC-SKEL
SL2325 RHEUMA
A1
9mm²
P
11.64mm
A1
RIGHT ULNAR ARM SAX
0
1
2

On 01/17/2018 patient underwent examination of multiple nerves in RUE and RLE as well as neck by Esaote MyLabAlpha ultrasound machine. The study revealed mainly focal hypoechoic enlargement of multiple nerves at the common entrapment sites, including right median at the wrist, right ulnar at the elbow, right ulnar at the wrist, right fibular nerve at the popliteal area (slightly hypoechoic), right tibial nerve at the ankle (slightly hypoechoic). The study also showed very mild focal enlargement of right tibial nerve at the popliteal area (with essentially normal echogenicity) and right median nerve at the elbow (with essentially normal echogenicity) and borderline right median nerve in the arm. Right C5 and right C6 cervical roots were of normal size. Right vagal nerve and right sural sensory nerve cross sectional area was also normal.

Per recent research studies published by Alexander Grimm, I calculated Ultrasound pattern sum score (UPSS) that for this patient was 6 points (including UPS-A score for peripheral nerves that was 6 points and UPS-B was 0 points and UPS-C was 0 points). According to research by A. Grimm et al, UPSS of more than 10 points and/or UPS-A of >=7 points suggest CIDP. Additionally, based on Grimm's UPS research, UPSS<= 10, UPS-A <=7, and UPS>=1 is suggestive of GBS. UPSS<= 3 is suggestive of axonal neuropathy.

In this ultrasound evaluation, the homogeneity score (HS) for right ulnar (0), median (0) and tibial (1) was 1 (per Grimm's research, HS of >=4 suggests CMT). Regional nerve enlargement index (RNEI) was low at 1 (right median nerve 1, right ulnar nerve 0, right tibial nerve 0). Entrapment score of right median nerve at the carpal tunnel (wrist to forearm ratio) was 2.57 (2 points). Entrapment ratio of right ulnar nerve at cubital tunnel (cubital to humerus ratio) was 2.22 (2 points). Grimm in his studies found that patients with HNPP (hereditary neuropathy with liability to pressure palsies) can have relatively low UPS scores, but entrapment ratios are >1.4 and entrapment score are >3.5. However, enlargement of nerves at the common entrapment sites can be seen in HNPP but can also be seen in multiple entrapment neuropathies.

For calculations as above I used the following CSA for the following nerves:

1. R Median n upper arm - 10 mm2 (1)
2. R Median n elbow - 13 mm2 (1)
3. R Median n forearm - 7 mm2 (0)
4. R Ulnar n upper arm - 9 mm2 (0)
5. R ulnar n forearm - 5 mm2 (0)
6. R tibial n popliteal - 33 mm2 (1)
7. R tibial n ankle - 17 mm2 (2)

8. R fibular n popliteal - 17 mm2 (1)
9. Vagal n carotid sheath - 3mm2 (0)
10. R C5 LAX transverse process - 2.6 mm distance (0)
11. R C6 LAX transverse process - 2.9 mm distance (0)
12. R sural nerve calf - 3 mm2 (0)

Additionally, the following measurements of CSA were done:

1. R median n wrist - 18 mm2 (hypoechoic)
2. R ulnar n hook of hamate- 6 mm2 (normal echogenicity)
3. R ulnar n wrist at pisiform bone - 9 mm2 (slightly hypoechoic)
4. R ulnar n medial epicondyle (ulnar groove) - 20 mm2 (hypoechoic)

Neuromuscular ultrasound evaluation of multiple nerves in right upper extremity, right lower extremity and right neck is suggestive of mainly hypoechoic enlargement of multiple nerves at common entrapment sites as described above that could be seen in multiple focal entrapment neuropathies but also in inherited neuropathies such as HNPP (Hereditary neuropathy with liability to pressure palsies). Clinical correlation is required. Additionally, mild nonspecific enlargement of right median nerve at the elbow and arm as well as borderline enlargement of right tibial nerve at the popliteal area was found and these are of unclear clinical significance at this time. Ultrasound findings were not suggestive of nerve enlargement patterns that can be seen in CIDP or inherited demyelinating polyneuropathy such as CMT1A but clinical correlation is required.

Summary

Positive result. Pathogenic variant identified in PMP22.
Variants of Uncertain Significance identified in IGHMBP2 and LITAF.
Indeterminate result: Variant identified in SMN1 or SMN2.

Gene	Variant	Zygosity	Variant Classification
PMP22	Deletion (Entire coding sequence)	heterozygous	PATHOGENIC
IGHMBP2	c.2755C>A (p.Arg919Ser)	heterozygous	Uncertain Significance
LITAF	c.424C>T (p.Gln142*)	heterozygous	Uncertain Significance
SMN1 or SMN2	c.770_780dupCTGATGCTTTG (p.Gly261Leufs*8)	unknown	Uncertain Significance

A Pathogenic variant, Deletion (Entire coding sequence), was identified in PMP22.
A deletion of the entire PMP22 gene is associated with autosomal dominant hereditary neuropathy with liability to pressure palsies (HNPP).
Approximately one-fifth of affected individuals are found to have a de novo mutation.

Hereditary Neuropathy with Liability to Pressure Palsies (HNPP):

- Autosomal Dominant inheritance
- Mainly PMP22 gene deletion (rarely associated with PMP22 sequence alterations)
- Characterized by acute, painless, and recurrent mononeuropathies (provoking factors: minor trauma or compression)
- Electrophysiological pattern of HNPP: increased distal motor latencies; normal or mildly reduced conduction velocities of other segments of motor nerves; a diffuse reduction in sensory nerve action potential, and focal slowing at multiple sites of entrapment.

Neurol Res. 2015 Feb;37(2):106-11. doi: 10.1179/1743132814Y.0000000411. Epub 2014 Jul 9.

Ultrasonographic findings in hereditary neuropathy with liability to pressure palsies.

Bayrak AO, Bayrak IK, Battaloglu E, Ozes B, Yildiz O, Onar MK.

- **Nerve enlargement was often identified in the median, ulnar, and peroneal nerves at the typical sites of compression (the wrist, elbow, and fibular head, respectively) .**
- None of the patients had nerve enlargement at a site of non-compression.
- None of the tibial nerves had increased CSA values at the malleolus.
- Although multiple nerve enlargements at typical entrapment sites were the main sonographic finding, **some patients had a normal sonographic evaluation despite clinical and electrophysiological findings of HNPP**.
- **Sonographic findings at entrapment sites showed similar features to those of idiopathic compression neuropathies.**

J Peripher Nerv Syst. 2012 Dec;17(4):391-8. doi: 10.1111/j.1529-8027.2012.00437.x.

Sonographic and electrodiagnostic features of hereditary neuropathy with liability to pressure palsies.

Ginanneschi F[1], Filippou G, Giannini F, Carluccio MA, Adinolfi A, Frediani B, Dotti MT, Rossi A.

- US nerve enlargements were only observed at sites where peripheral nerves tend to be entrapped in otherwise normal people, such as the carpal tunnel, the elbow, the fibular head and Guyon's canal. This increased nerve CSA in common sites of nerve entrapment likely reflected the well-documented nerve vulnerability to mechanical stress in HNPP

- Conclusion: **ultrasonography alone cannot be used as a diagnostic tool for HNPP**. If there is diagnostic difficulty, ultrasonography may contribute to the differential diagnosis of HNPP and other demyelinating polyneuropathies in which diffuse nerve enlargements have been observed.
- In addition, we usually observe a correlation between electrophysiological and sonographic findings in patients with compression neuropathies in our daily practice; **if there is no such correlation in a patient who is being investigated for a compression neuropathy, or if multiple enlargements are seen at entrapment sites, then HNPP must be suspected.**