Are Nerve Biopsies Including Targeted Fascicular Nerve Biopsies Useful in Modern Clinical Practice?

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None

Learning Objectives

- To determine whether nerve biopsies are still clinically useful and justifiable.
- To determine the role of targeted fascicular nerve biopsy from sites of MRI lesions.

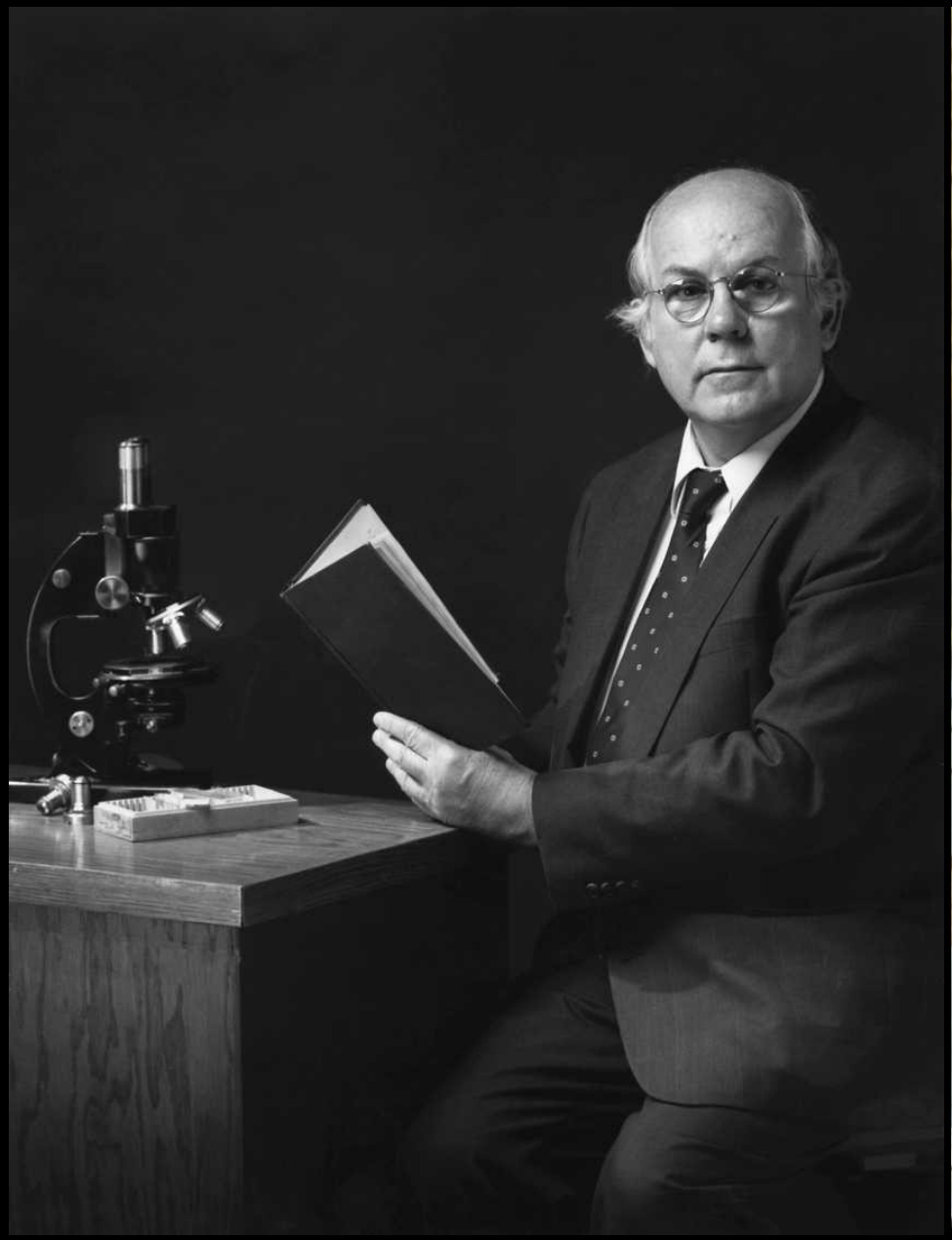
Introduction

- Nerve biopsy has been historically important in evaluation of patients with peripheral neuropathy.
- The practice of nerve biopsy is on the decline because of better laboratory, radiographic and electrophysiologic testing and better understanding of disease pathophysiology.
- Some experts have questioned if there is an ongoing need for nerve biopsy.

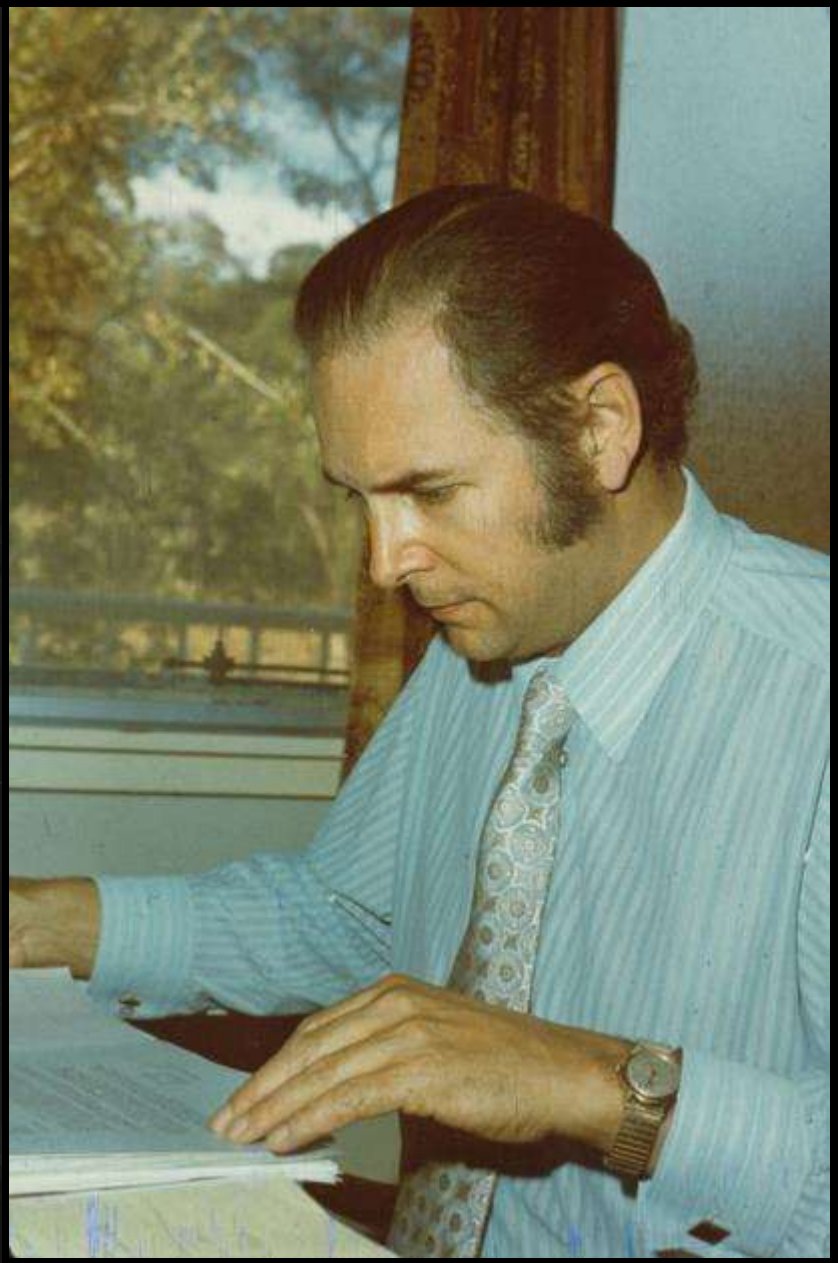
Historical Perspective

- The use of nerve biopsy is relatively recent.
- German neuropathologists in 1800s looked at autopsy nerve specimens.
- In the mid 1960s, Dr. Peter J. Dyck (Mayo) and Dr. P. K. Thomas (London) introduced the systematic use of nerve biopsy with standardized techniques.

Dr. P. J. Dyck

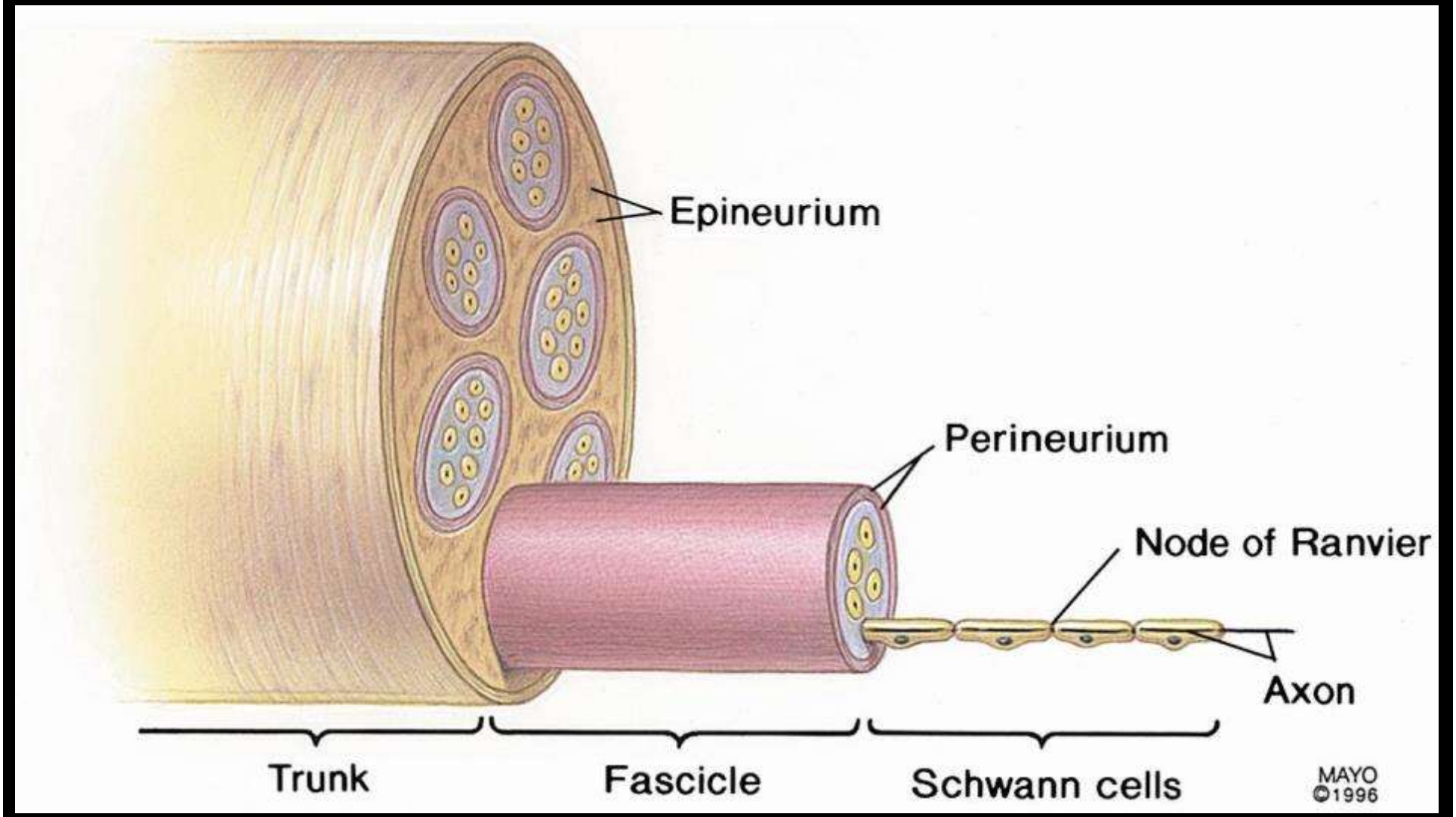


Dr. P. K. Thomas



Historical Perspective

- Traditionally, nerve biopsy is taken from a cutaneous nerve (a sensory nerve located under the skin).
- The advantage of cutaneous nerve biopsies is that they give no motor deficits.
- The sural nerve is used most commonly because it is distal and is involved in most length dependent neuropathies.
- Side effects include sensory loss, pain and paresthesia.


Epineurium
Perineurium
Node of Ranvier
Axon
Trunk
Fascicle
Schwann cells
MAYO
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Standard Nerve Biopsy Preparations

- Multiple preparations should be standardly performed:
  - Teased fiber preparations: best way to follow nerve fibers longitudinally.
  - Paraffin sections: cross and longitudinal, stained with H & E, trichrome, LFB/PAS, Congo Red and methyl violet (amyloid stains) and Turnbull Blue (hemosiderin stain).
  - Paraffin sections for immunohistochemistry: LCA (CD45) for leukocytes, KP-1 (CD68) for macrophages, S-100 (Schwann cells), EMA (perineurial cells) and SMACTIN (smooth muscle actin) for disruption of vessel walls.

Standard Nerve Biopsy Preparations (cont.)

- Epoxy semithin sections stained with methylene blue: good for judging density of myelinated fibers, size distribution, onion-bulb formation, etc.
- Epoxy thin sections for electron microscopy: done to look at small myelinated and unmyelinated fibers, axonal inclusions and other ultrastructural features.

Reasons to do a Nerve Biopsy

- Sometimes a suspected diagnosis can only be made by a pathological nerve specimen.
  Examples include:

necrotizing vasculitis	lymphoma
sarcoidosis	perineurioma
amyloidosis	metastatic tumors
leprosy	other

- The potential gains of a nerve biopsy should outweigh the potential side effects.
- The neuropathy is severe or rapidly worsening.

Selecting a Nerve to Biopsy

- The nerve biopsied needs to be clinically involved.
- The sural nerve may not be involved if the process is predominantly motor, proximal, multifocal, or exclusively involves the upper limb.
- Other cutaneous sensory nerves that can be biopsied include the superficial peroneal, saphenous, superficial radial, antebrachial cutaneous, great auricular (neck) and others.
- Targeted fascicular biopsies from areas of imaging abnormalities are becoming an option.
- Biopsy sites need to be selected on a case by case basis.

Information Gained from Nerve Biopsy

- Nerve biopsies give information about:
  - nerve fibers themselves (neuropathic)
  - the interstitium

Neuropathic

- Although nerve biopsies give information about nerve fibers (axonal degeneration and segmental demyelination), most of this information can be inferred from nerve conduction studies and EMG.
- Few specific diagnoses are made from neuropathic abnormalities. Examples include polyglucosan body disease and HNPP.

Interstitial Abnormalities are Key

- The primary reason for a nerve biopsy is to understand the interstitial abnormalities.
- Interstitial abnormalities can only be found by directly viewing nerve tissue.
- Probably the most important interstitial abnormalities are the inflammatory/immune:
  - inflammatory demyelinating
  - vasculitis
  - microvasculitis
  - sarcoidosis
  - other
- Amyloidosis, leprosy, lymphoma and tumors are also found by examining the interstitium.

Whole Nerve Biopsy vs. Fascicular

- Advantages of whole nerve biopsy:
  - more nerve fibers and interstitium to assess
  - good for sensory or sensorimotor neuropathies
- Advantages of fascicular (partial) nerve biopsy:
  - only part of the nerve is removed and so the deficit/side effects are less
  - good for focal or motor neuropathies
- In general:
  - distal cutaneous nerve → whole biopsy
    - ~ usual technique and good for most neuropathies
  - proximal nerve → fascicular biopsy
    - ~ new technique and good for focal or motor neuropathies

Examples of Whole Distal Cutaneous Nerve Biopsies (Sensory Nerve Biopsies)

Case 1

- 14 year old girl with 4 year history of quadriparesis.
- Rapid paralysis with only eye movements preserved after a flu-like illness. She was intubated and ventilated for 1½ months. CSF protein 100 mg/dL. Diagnosed with AIDP.
- Mild improvement but wheelchair bound with limited use of hands.
- One year later, breathing worsened. Re-intubated and ventilated for 8 months.
- Treated with short courses of IVIg, prednisone and Cellcept without definite improvement.
- Unclear if weakness was residual deficit of AIDP or active CIDP.

Neurological Examination

- Reflexes were reduced in upper limbs, absent in lower limbs.
- Sensory examination showed reduced vibration in toes, otherwise normal.
- She was unable to walk.
- Neuropathy Impairment Score (NIS) was 82.5.

Muscle exam	
Deltoid	-2 / -3
Biceps	-2 / -3
Triceps	-2 / -3
Thenar	-2 / -3
Hypothenar	-2 / -2
Iliopsoas	-3 / -3
Gluteus Max.	-2 / -2
Quadriceps	-2 / -2
Hamstrings	-2 / -2
Ant. Tibial	-2 / -2
Gastroc.	-2 / -1

(-1=25%, -2=50%, -3=75% and -4=100% weak)

Nerve Conduction Studies

Stimulate (Record)	A (mV/μV)	CV (m/s)	DL (ms)	F (ms)
L. Median motor	0.9 (>4.8)	33 (>49)	12.0 (<4.2)	58.7
L. Median sensory	18 (>13)	38	5.1 (<3.5)	
L. Ulnar motor	2.4 (>5.8)	25 (>49)	6.3 (<3.8)	52.6
L. Ulnar sensory	11 (>7)	38	5.3 (<3.0)	
L. Sural sensory	0.0 (>1.3)		NR (<6.0)	
L. Peroneal motor (EDB)	0		NR	
L. Peroneal motor (TA)	1.0	9	7.6	
L. Tibial motor	0.0 (>5.8)		NR (<4.8)	

Blink Reflexes

	Ipsilateral R1	R2	Contralateral R2
L. Trigeminal supraorbital	19.2 (8-13)	38.0 (29-41)	39.3 (29-44)

Needle EMG

Muscle	Insertional activity	Fib	Fasc	Reduced recruit.	Long	High	Phases
L. Biceps	Normal	0	0	++	++	+	25%
L. FDI	Normal	0	0	++	++	++	
L. M Gast	Increased	0	0	++	++	++	25%
L. TFL	Normal	0	0	++	++		75%
L. TA	Increased	0	0	+++	++	+	25%
L. VM	Increased	0	0	++	++	++	50%

- Interpretation: A severe, generalized polyradiculoneuropathy with demyelinating features. There is no evidence to suggest an active or recently active process.

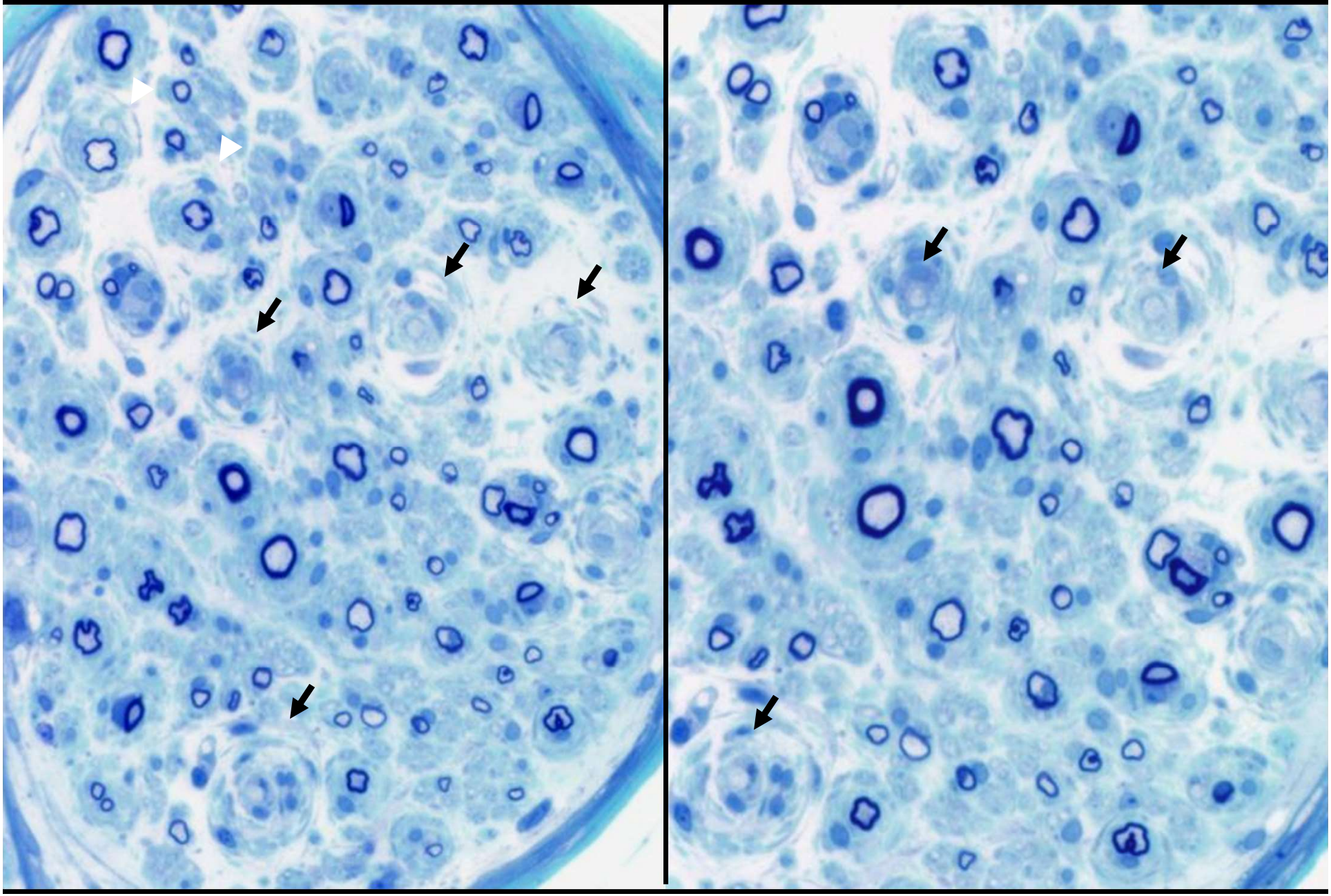
Evaluation

- Laboratory evaluations were normal
- QST was abnormal (pan-modality):
  VDT > 99th percentile
  CDT > 99th percentile
  HP:5.0 = 98th percentile
- Repeat CSF could not be performed because of severe scoliosis.
- Left whole sural nerve biopsy was performed to look for ongoing inflammatory demyelination.

Semithin Epoxy Section

Onion-bulbs

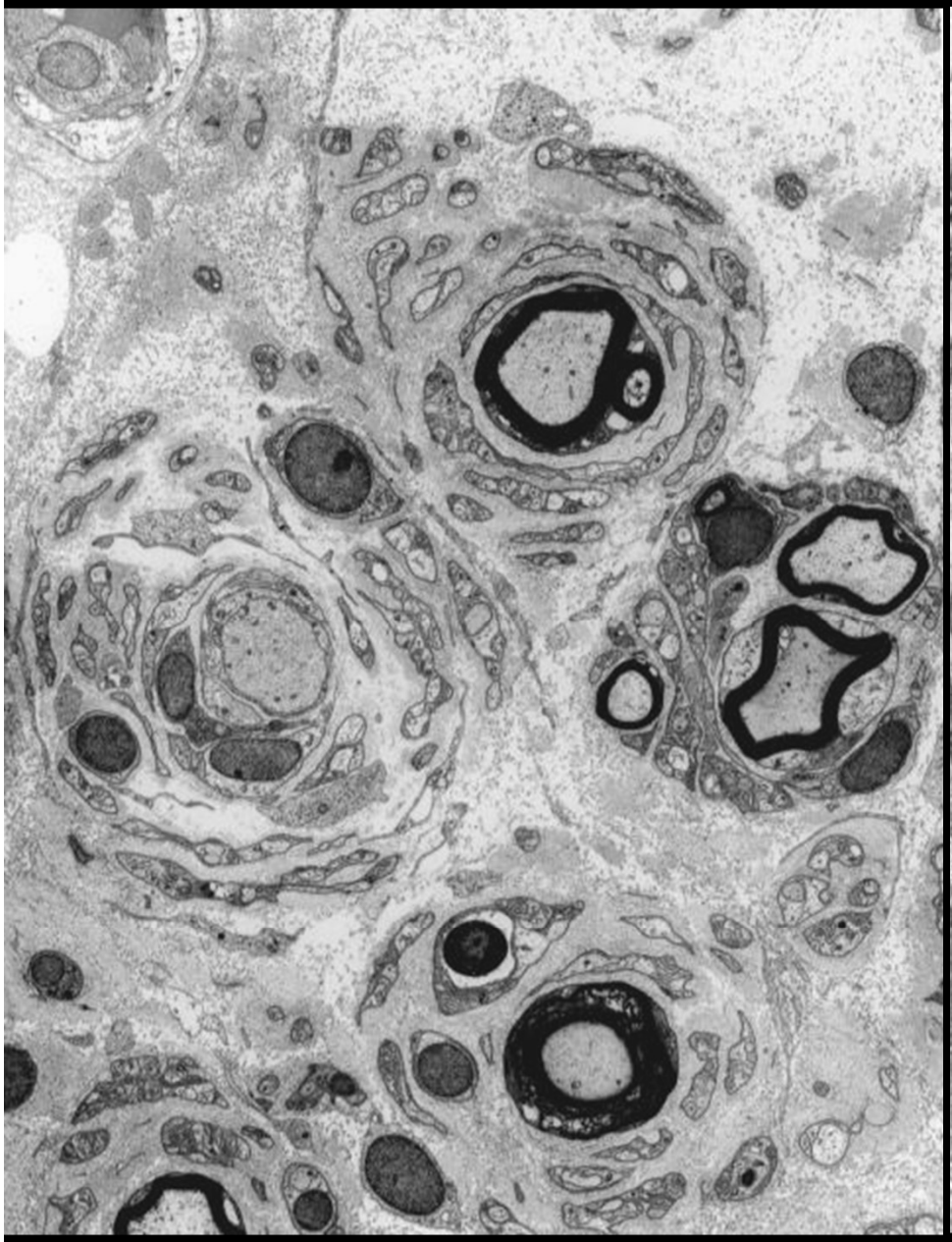
Naked Axons

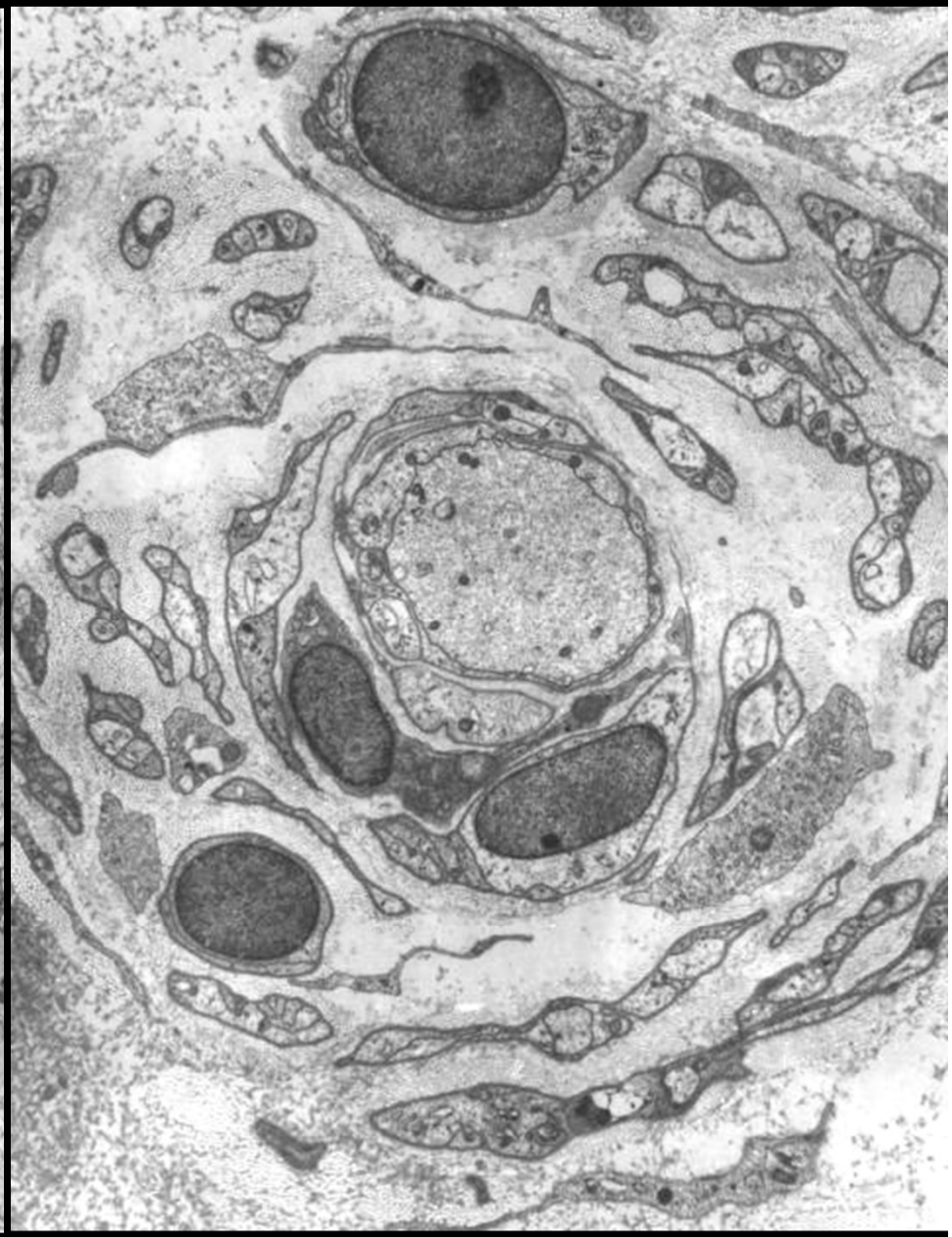


Electron Microscopy

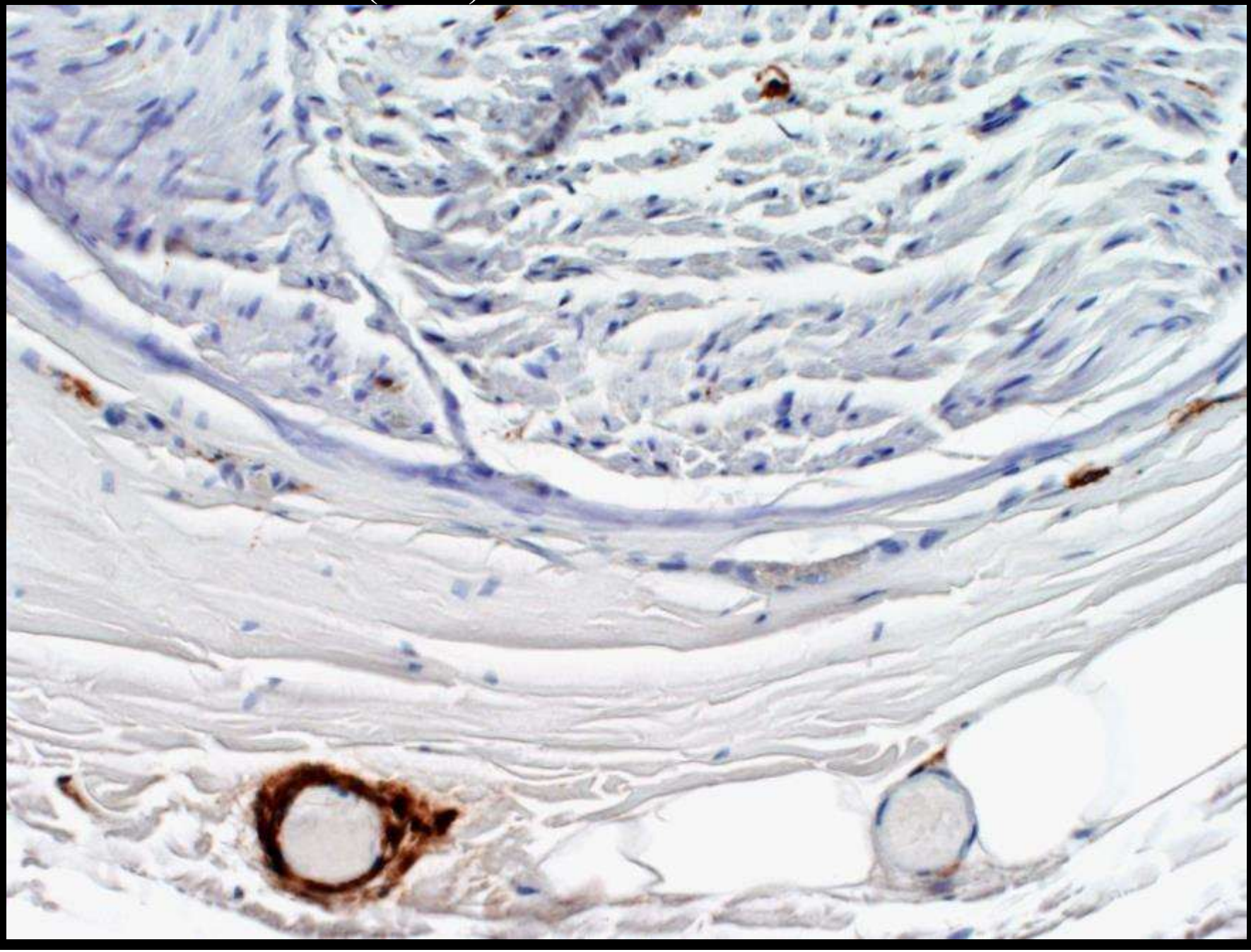
Onion-bulbs

Naked Axons





CD45 (LCA) – Perivascular Inflammation



Pathology Suggests Active Inflammatory Demyelination

- Increased demyelination (5%) and remyelination (49%) on teased fibers.
- Many onion-bulbs present: evidence of chronic de- and remyelination.
- Many naked axons present: active demyelination.
- Scattered endoneurial and epineurial perivascular mononuclear inflammatory cells.

Case 1: Outcome and Lessons

- IVIg twice weekly for 3 months and then once weekly. At 6 months, she felt 50% improved, used crutches to walk and began using her hands.
- At 1 year, she could walk without aids and was able to dress and feed herself.
- Nerve biopsy confirmed she had CIDP and not AIDP (active inflammatory demyelination) when the clinical history and evaluation could not.
- Findings of nerve biopsy directly resulted in aggressive long term immunotherapy and subsequent clinical recovery.

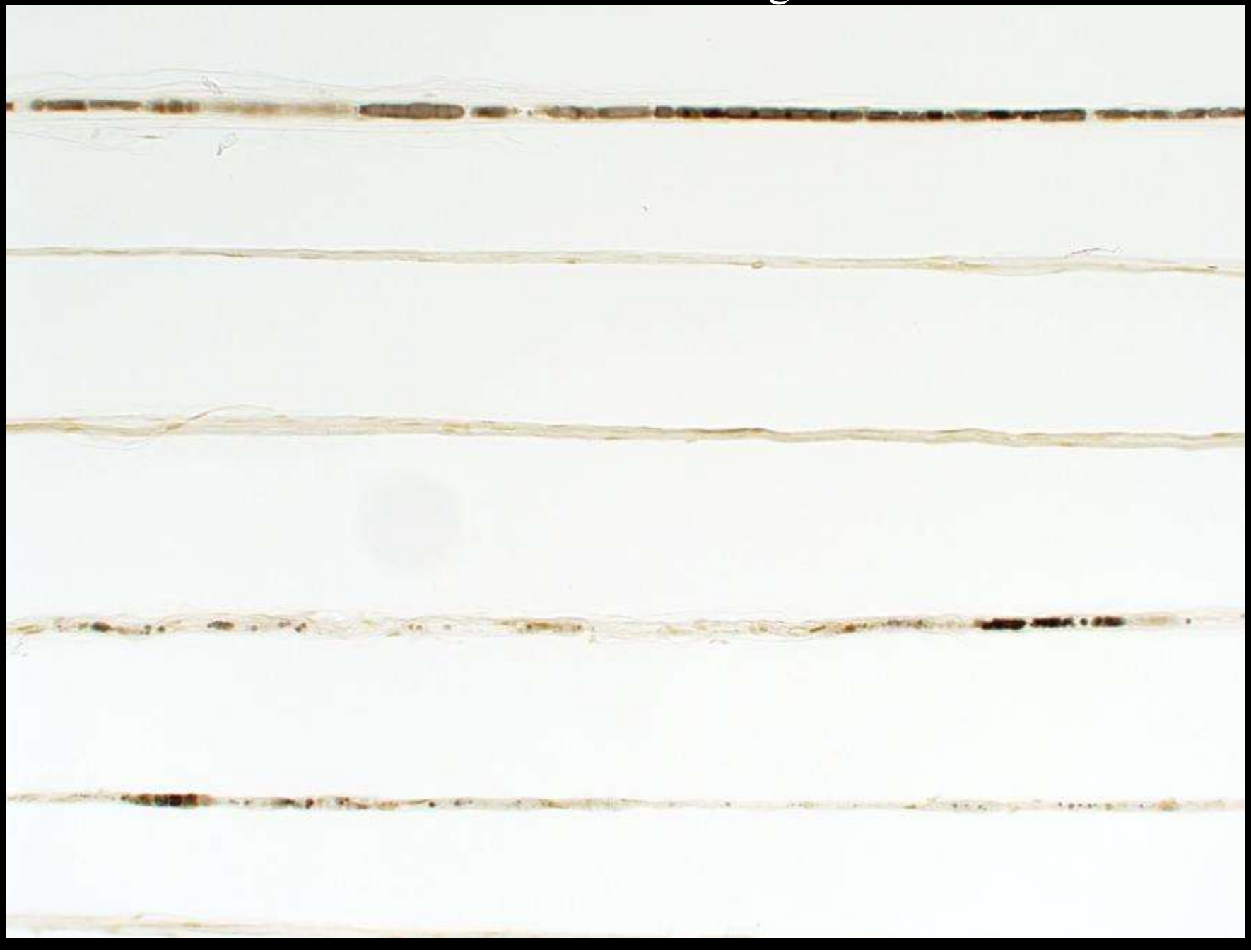
Case 2

- 60 year old man with DM type 2 presents with left and then right lower limb weakness over 11 months, now using a walker.
- His left leg pain and weakness were improving but his right foot drop and leg had recently developed.
- He had frequent falls, difficulty going up stairs and denied weight loss.
- PMHx thoracic radiculopathy (2 years earlier), diabetes mellitus type 2.

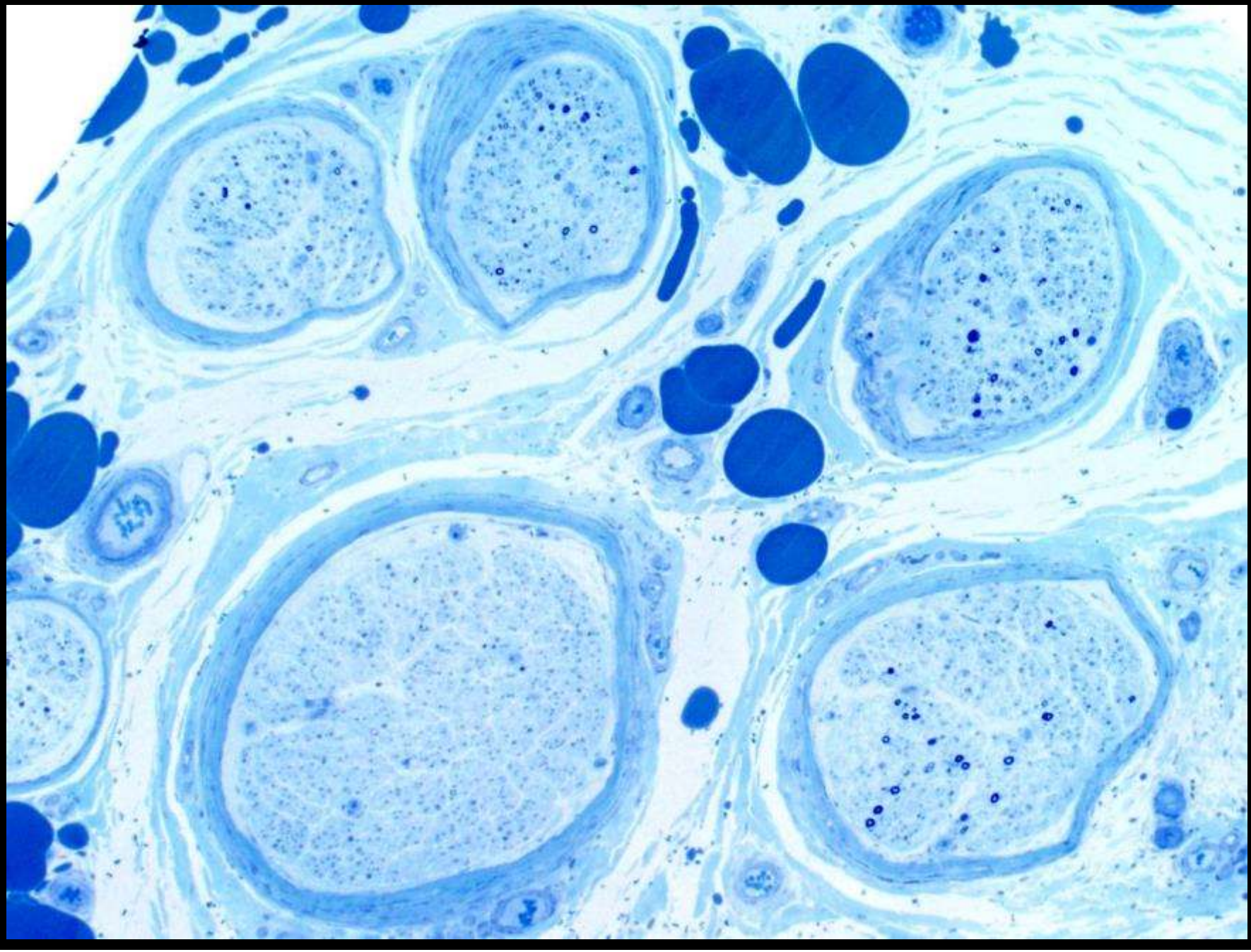
Case 2 - Evaluation

- QST showed small fiber abnormality:
  VDT: Normal
  CDT > 99th percentile
  HP:5.0 > 99th percentile (insensitive)
- MRI of LS spine and LS plexus were unremarkable.
- CSF: 1 WBC, protein 97 mg/dL, glucose 84 mg/dL, negative cytology.
- NCS/EMG showed a severe right lumbosacral plexopathy superimposed on a possible generalized neuropathy.
- Clinical diagnosis: diabetic lumbosacral radiculoplexus neuropathy (DLRPN).
- Unclear if clinical impairment was from residual injury or ongoing microvasculitis and ischemic injury.

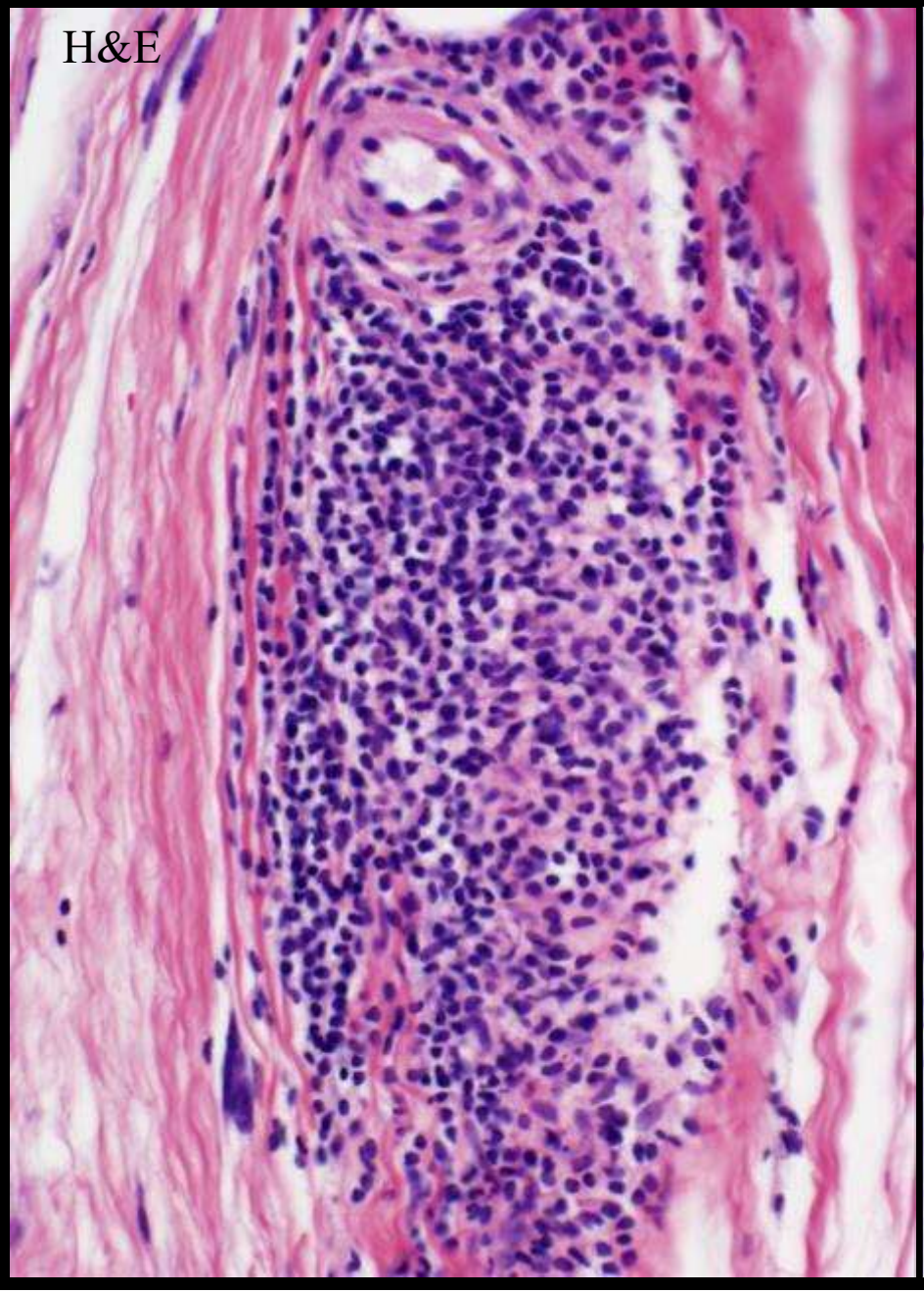
Teased Fibers – Axonal Degeneration

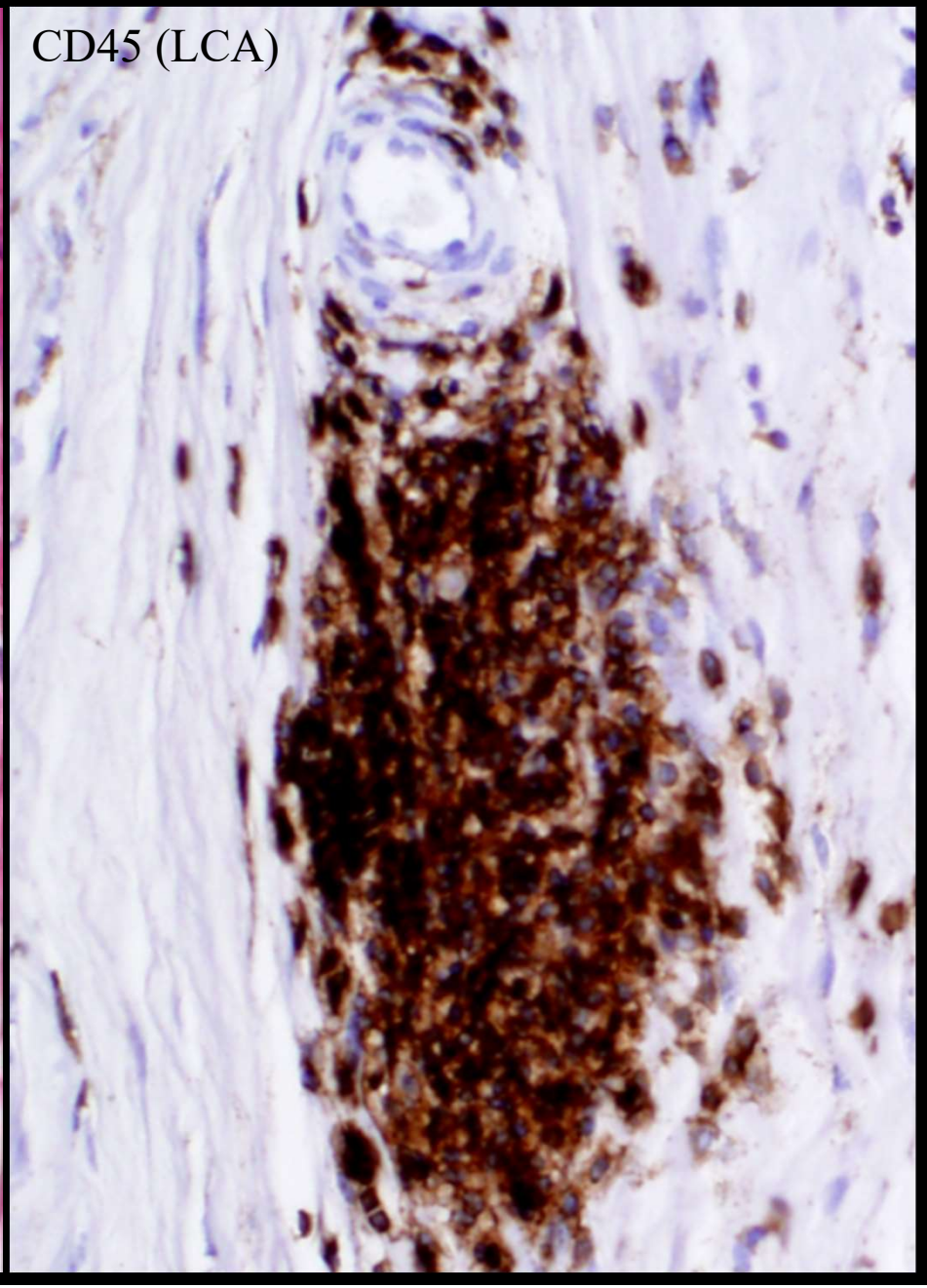


Severe and Multifocal Fiber Loss

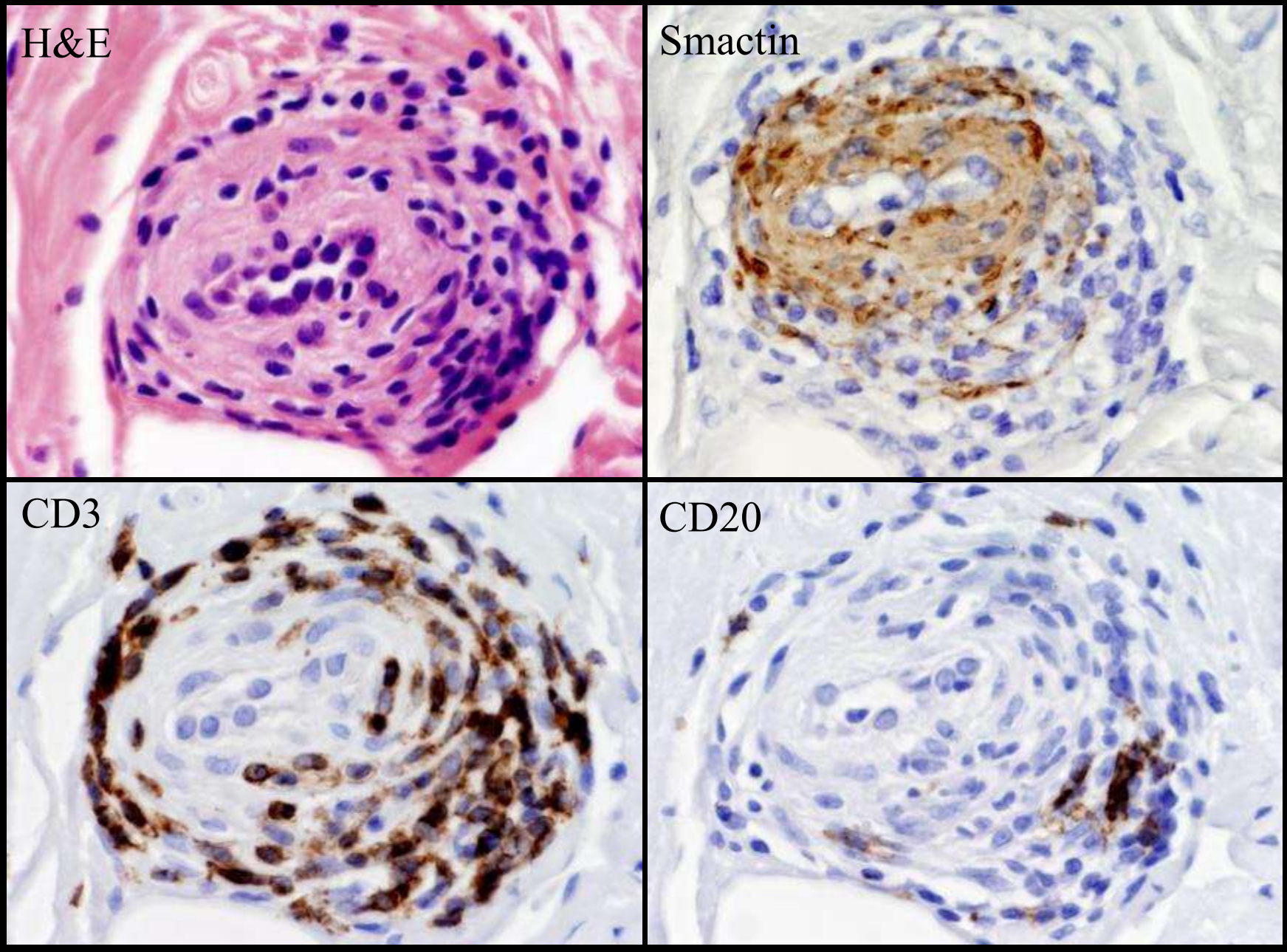


Large Perivascular Inflammatory Collections





Microvasculits



Pathology Showed Active Microvasculitis

- Increased axonal degeneration (67%) and empty nerve strands.
- Evidence of ischemic injury: severely reduced density of myelinated fibers (multifocal), neovascularization and perineurial thickening (ischemic injury).
- Large perivascular inflammatory cell collections and hemosiderin laden macrophages.
- Diagnostic of ischemic injury and microvasculization.

Case 2: Outcome and Lessons

Nerve Biopsy Can Show a Disease is Active

- The biopsy showed that the disease process was still active with ischemic injury and microvasculitis.
- The patient was treated with IV methylprednisolone 1.0 gm weekly for 12 weeks. His pain resolved and his weakness improved. He went from using a walker to walking independently.

Case 3

- 60 year old man with IgM MGUS and asymmetrical weakness worsening over 4 years.
- 4 years earlier, developed left foot drop;
  2 years earlier, developed left arm weakness; and
  1 year earlier, right foot drop with shooting pain.
- IgM Kappa MGUS diagnosed and bone marrow bx negative for Waldenstrom's.
- He was diagnosed as CIDP.
- Treated with PLEX for 11 treatments with neurological worsening, followed by monthly IVIg with worsening right arm strength.

Nerve Conduction Studies

Stimulate	(Record)	AMPLITUDE (milli/micro)volts			VELOCITY meters/sec.			DISTAL LATENCY milliseconds			F-WAVE LATENCY milliseconds	
		right	left	normal	right	left	normal	right	left	normal	right	left
Median, motor	(Abductor pollicis br)	-	9.0	(>4.0)	-	55	(>48)	-	4.0	(<4.5)	-	28.6
Median, sensory	(Index)	23	- 9	(>15)	-	61	(>56)	2.9	- 2.9	(<3.6)	-	
Radial, sensory	(Dorsal hand)	10	- 19	(>20)	-		(>49)	2.4	- 2.3	(<2.9)	-	
Ulnar, motor	(Abductor digiti mini)	-	10.5	(>6.0)	-	58	(>51)	-	2.9	(<3.6)	-	28.3
Ulnar, sensory	(Fifth)	-	38	(>10)	-	61	(>54)	-	2.9	(<3.1)	-	
Peroneal, motor	(Extensor digitorum b)	3.7	- 0.0	(>2.0)	48	-	(>41)	6.3	- NR	(<6.6)	55.9	-
Peroneal, motor	(Tibialis anterior)	-	0.2		-	33		-	5.3		-	
Sural, sensory	(Ankle)	4	- 6	(>6)	-	46	(>40)	4.2	- 4.1	(<4.5)	-	
Tibial, motor	(Abductor hallucis)	-	0.5	(>4.0)	-	37	(>40)	-	7.7	(<6.1)	-	NR
Lateral antebrachial, sensory	(Forearm)	9	- 0		-			2.2	- NR		-	

Needle EMG

VOLUNTARY MOTOR UNIT POTENTIALS

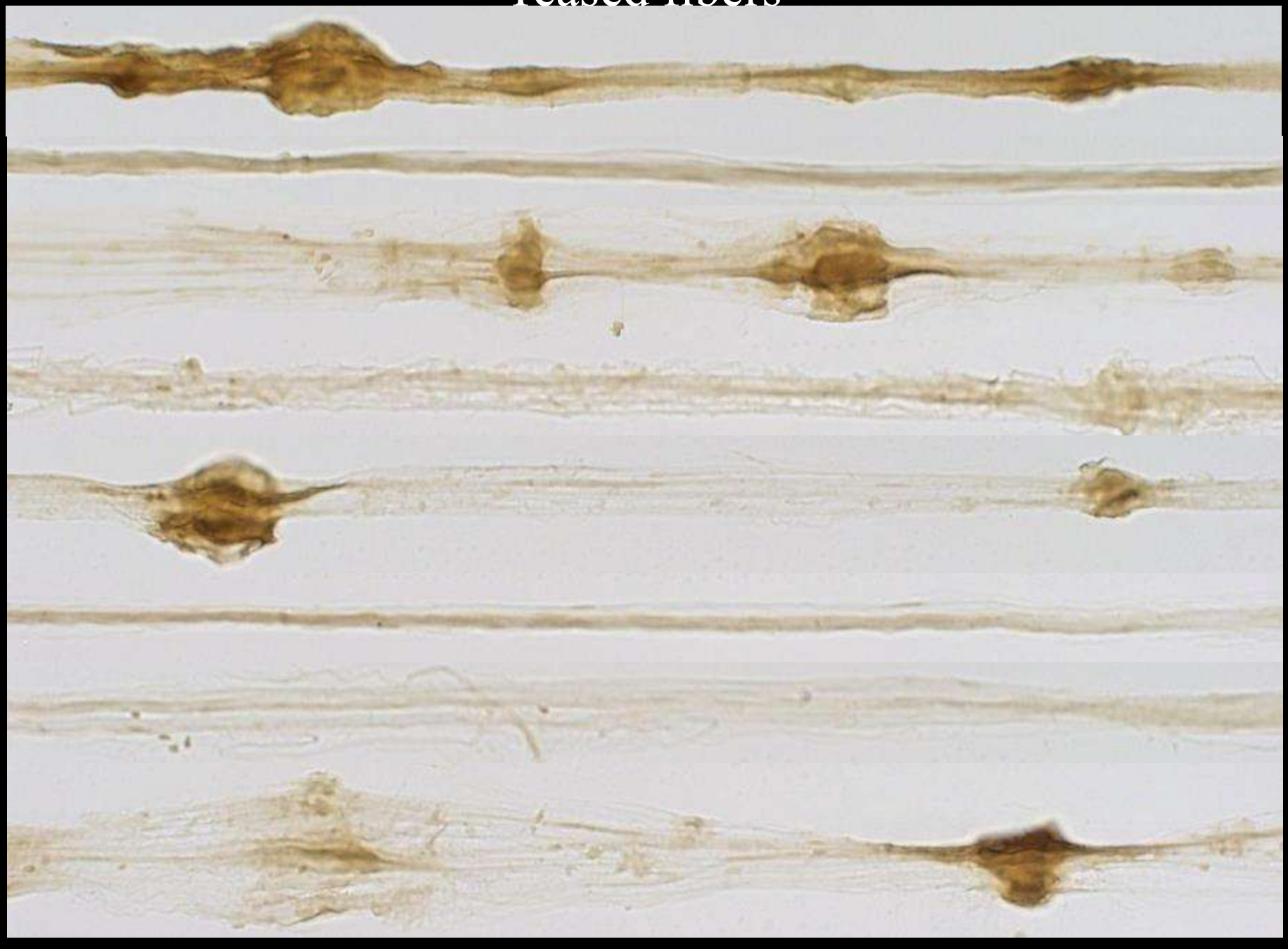
MUSCLE	INSERT. ACTIVITY	SPONTANEOUS Fib.	SPONTANEOUS Fasc.	MUP NORMAL	RECRUITMENT Act.	RECRUITMENT Reduced	RECRUITMENT Rapid	DURATION LONG	DURATION SHORT	AMPLITUDE HIGH	AMPLITUDE LOW	PHASES %	TURNS
L. Biceps brachii	Increased	++	0			+++		++		++		100%	++
L. Deltoid	Increased	++	0			++		+++		+++			
L. First dorsal interosseous	Normal	0	0	Normal									
L. Pronator teres	Increased	+++	0			+++			+		+		
Comment: few nascent units													
L. Triceps brachii	Increased	+/-	0			+		++		++		75%	++
L. Biceps femoris (long head)	Normal	0	0					+		+		15%	
L. Biceps femoris (short head)	Normal	0	0					+		+		25%	
L. Gluteus maximus	Normal	0	0	Normal									
L. Gluteus medius	Normal	0	0	Normal									
L. Medial gastroc.	Inc/Dec	0	0										
Comment: distan units; essentially no activation													
L. Tensor fasciae latae	Normal	0	0	Normal									
L. Tibialis anterior	Increased	++	0		None								
L. Vastus medialis	Normal	0	0	Normal									
L. Cervical paraspinals	Normal	0	0					+/-		+/-		15%	
L. Thoracic paraspinals	Normal	0	0	Normal									

Interpretation: There was a multifocal, asymmetric, axonal, sensorimotor neuropathy with predominant involvement in left sciatic and brachial plexus without root involvement.

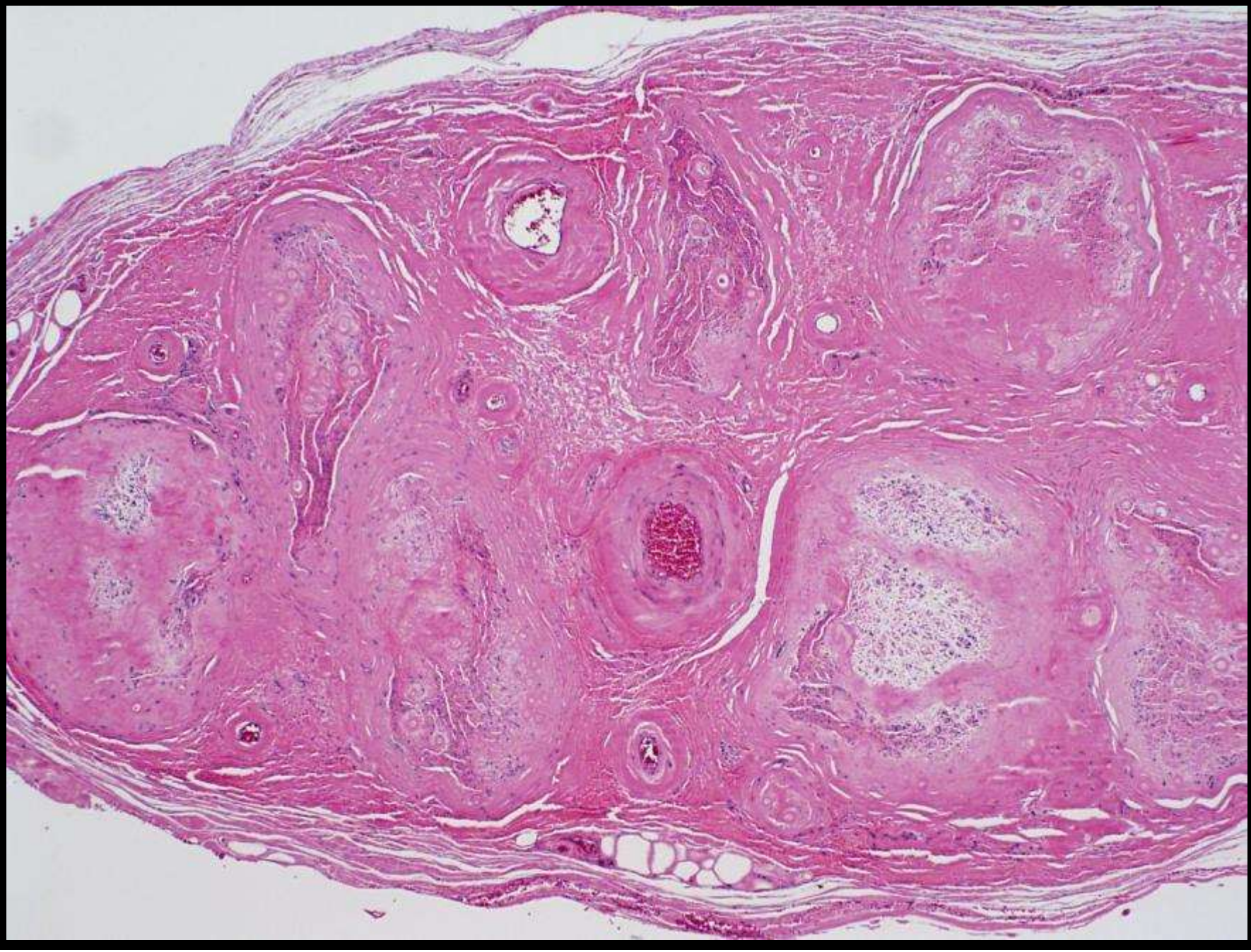
Case 3 - Evaluation

- QST: Panmodal sensory loss (touch vibration, cooling, heat pain all reduced in foot).
- Bone marrow biopsy: 5 % kappa light chain, restricted plasma cells.
- Fat aspirate and echocardiogram: Normal.
- MRI of plexus: Mild focal enlargement and minimal increased T2 signal in upper trunk, non-specific inflammation.
- CSF: Protein 115 mg/dL, glucose 57 mg/dL, WBC 4.
- Sural nerve biopsy performed.

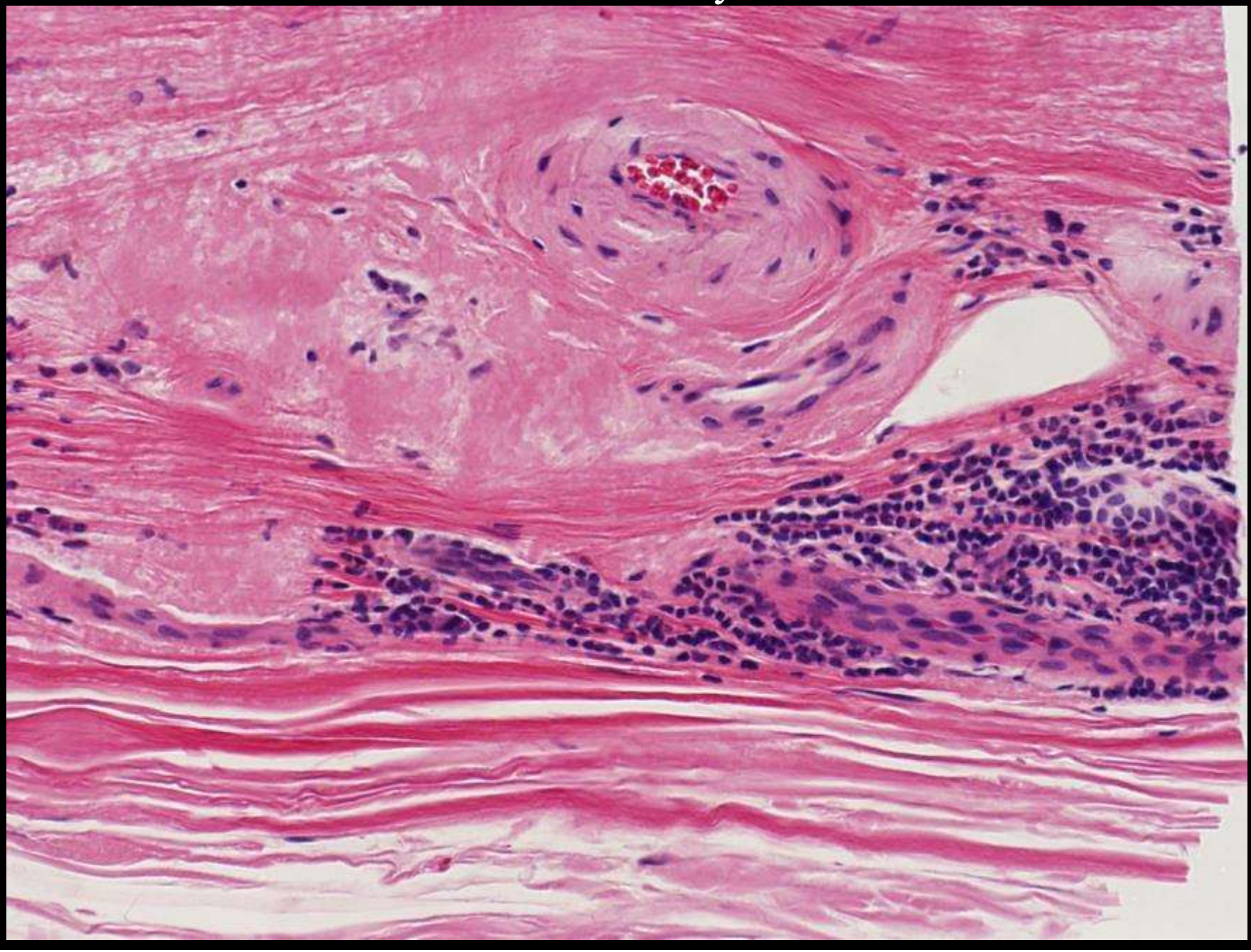
Teased fibers



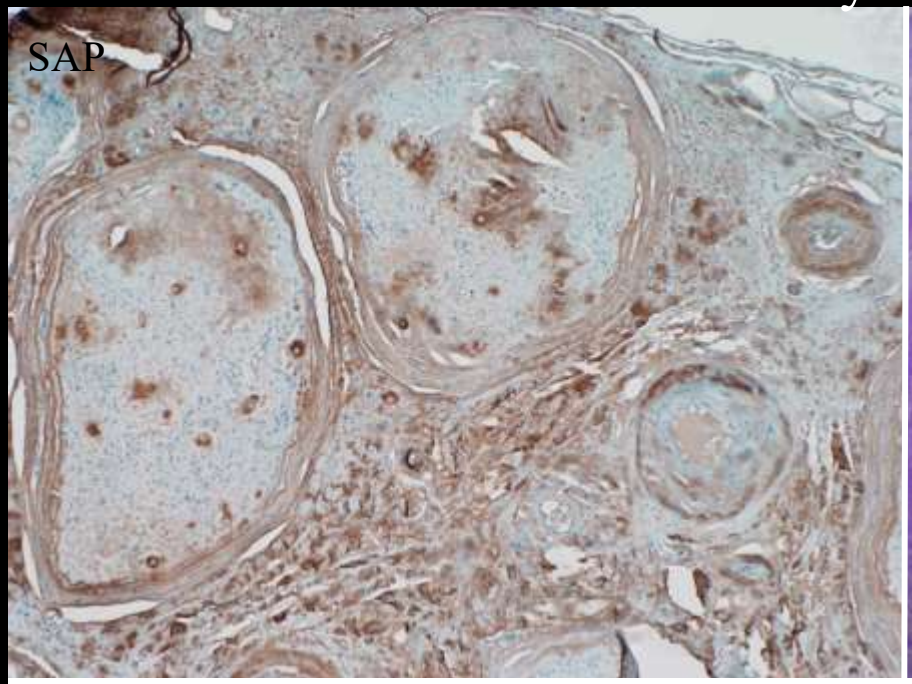
H&E

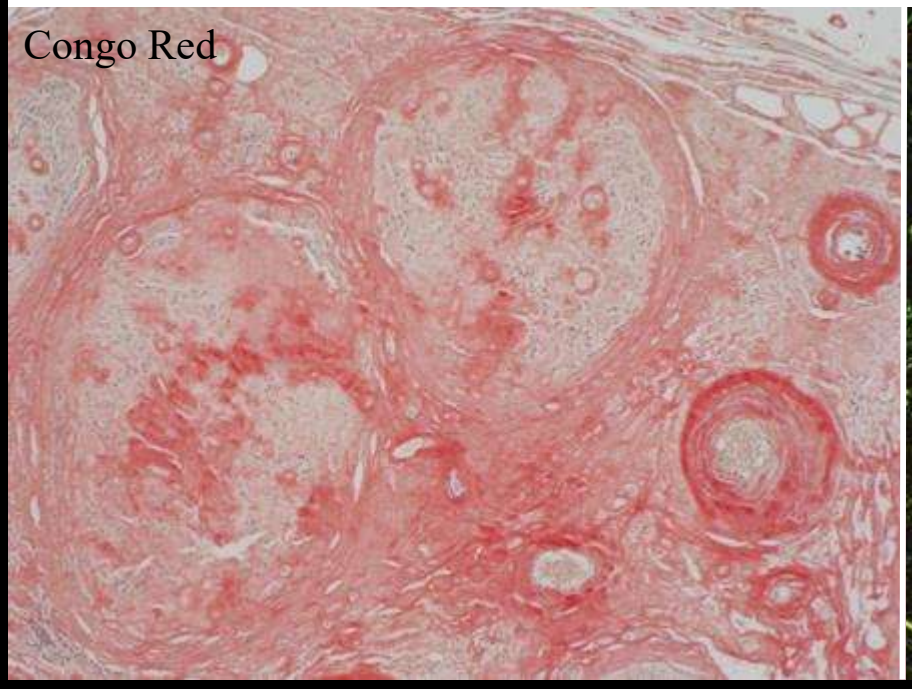


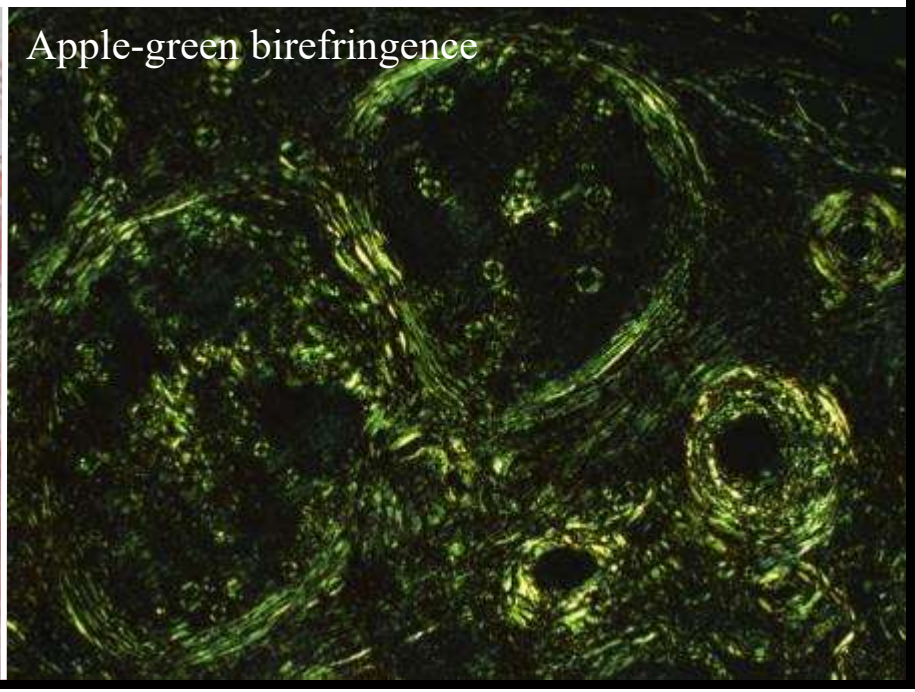
H&E – Inflammatory Infiltrate



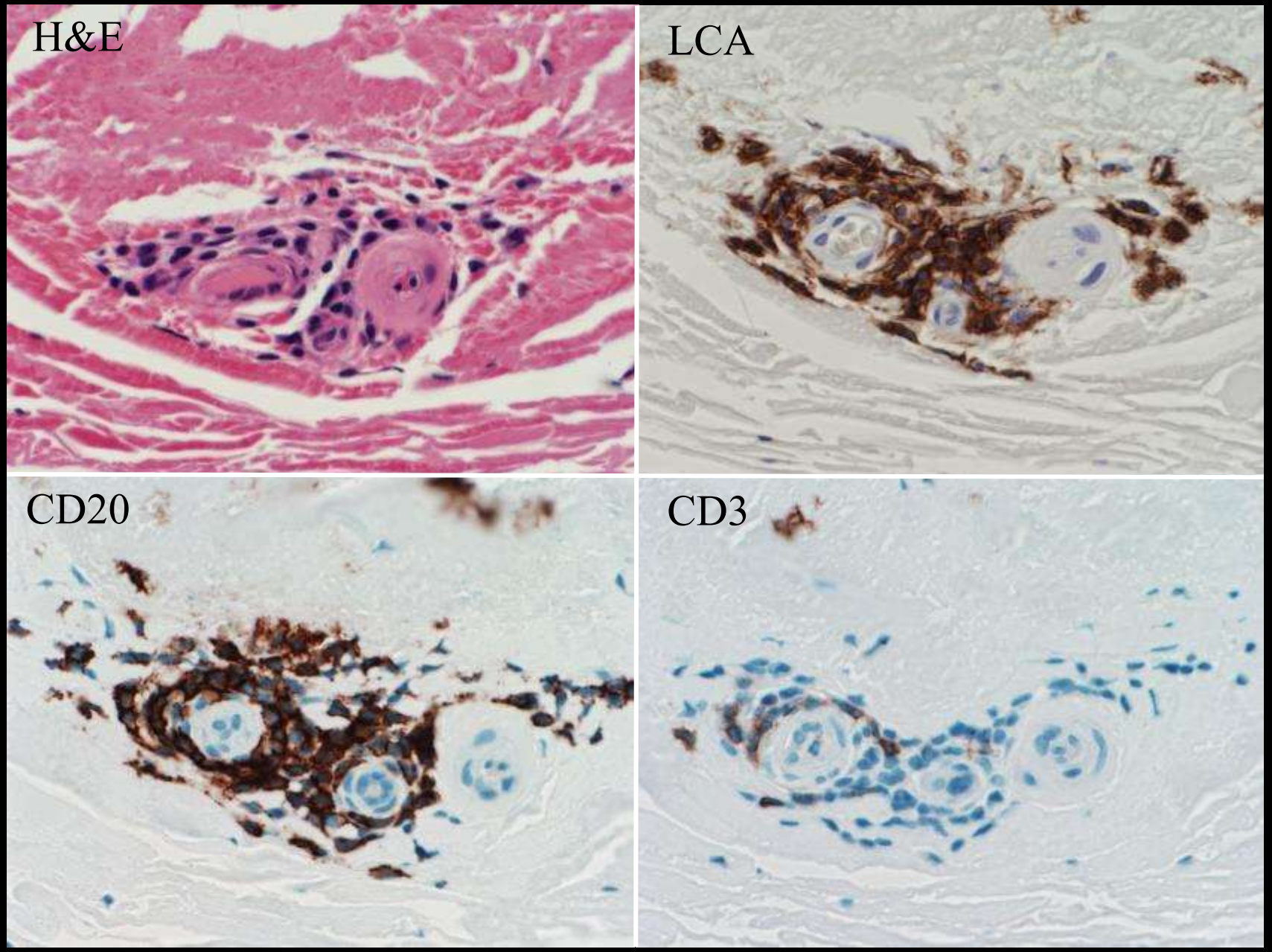
Amyloidosis







B-cell Disorder



Pathology

- Increased empty nerve strands and severe reduced density of myelinated fibers.
- Amyloid deposition in epineurium, perineurium and endoneurium.
- Inflammatory infiltration that have prominent CD20 (B-cell) reactivity and little CD3 (T-cell) reactivity.
- Mass spectroscopy confirmed AL (Kappa) type amyloid deposits.
- Final diagnosis:
  - Low grade B-cell lymphoma
  - AL (Kappa) amyloidosis.

Case 3: Outcome and Lessons

- This nerve biopsy provided two diagnoses
  - Amyloidosis
  - Low-grade B-cell lymphoma
- Blood and bone marrow evaluations failed to make these diagnoses.
- The nerve biopsy changed management and provided justification to start patient on chemotherapy.
- The patient's neuropathy course stabilized.

Case 4

- 47 year old woman with 2 years of numbness of lips and nose and 3 months of numbness and burning of the feet.
- Her gait was unsteady and she fell.
- She had dry mouth, excessive thirst and red irritated eyes.
- Outside MRI of lumbar spine showed mild enhancement of the cauda equina.
- Outside CSF showed protein 132 mg/dL, 41 WBCs and negative cytology.

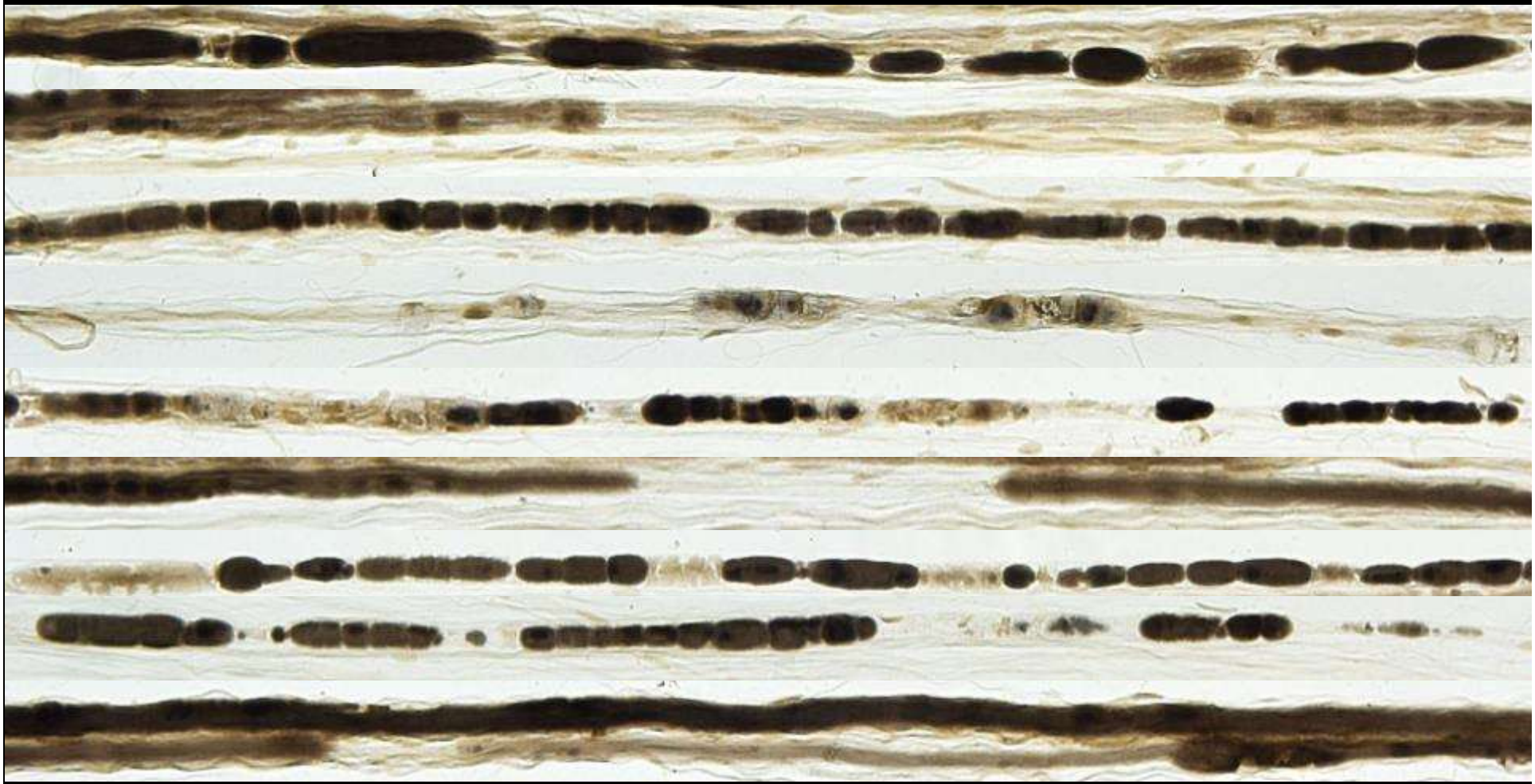
Neurological Examination

- Her strength showed distal lower limb weakness.
- Reflexes were reduced at the ankles.
- Sensory examination showed pan-modality sensory loss at the feet (touch, vibration, pin-prick and joint position sense) and reduced pin periorally in the face.
- Her gait was ataxic and she had a Romberg sign.
- Eye exam confirmed dry eyes.

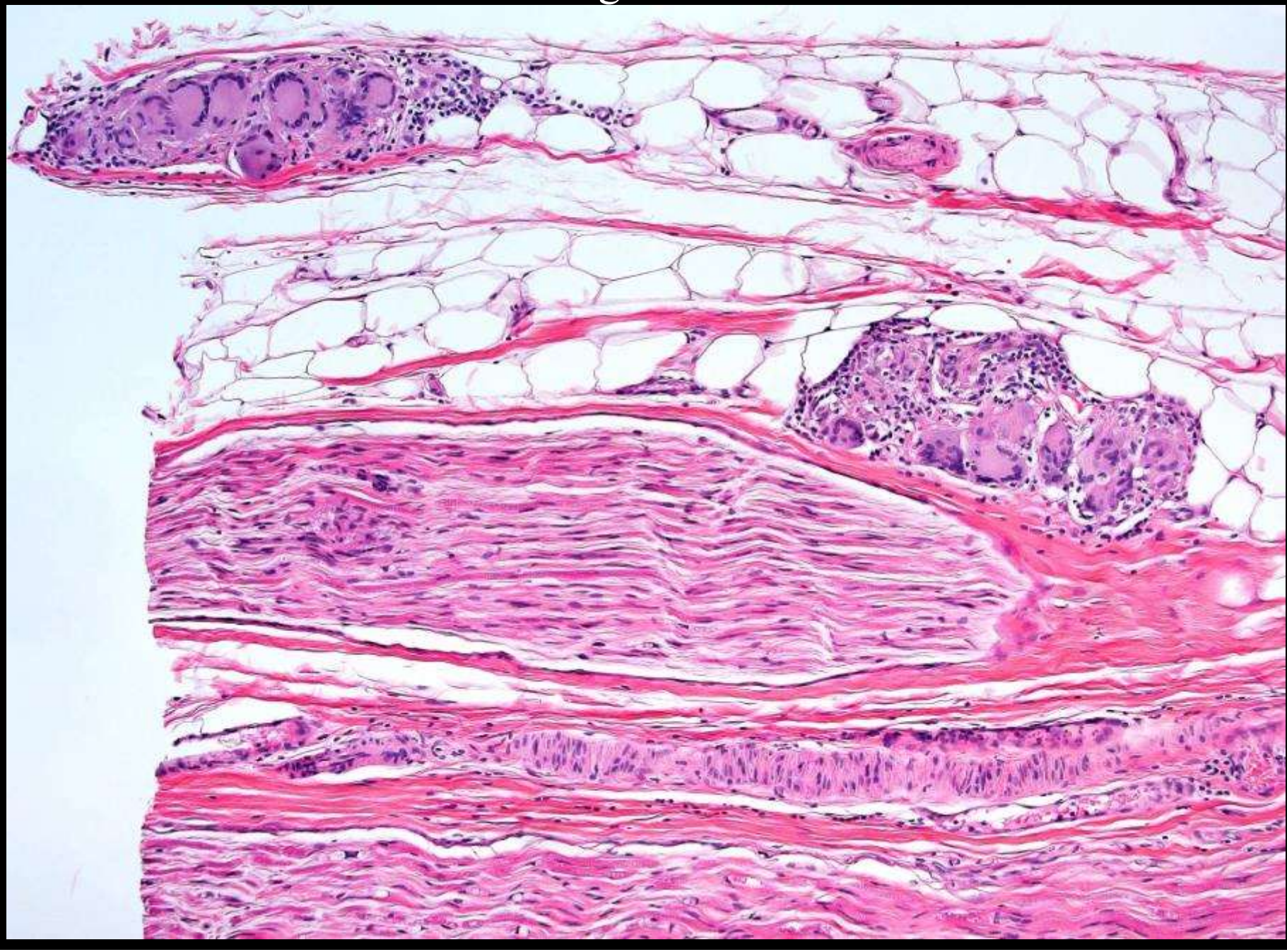
Evaluation

- NCS/EMG showed a length dependent sensorimotor peripheral neuropathy and lumbosacral paraspinal fibrillations.
- QST showed reduced vibration in the feet.
- Thermoregulatory sweat test showed patchy sweating loss in right leg and left arm.
- CSF protein 91 mg/dL, glucose 64 mg/dL and 14 WBC.
- Paraneoplastic antibodies and rheumatological tests were negative; ACE = 22 U/L (<22).
- We suspected Sjögren's neuropathy (dry eyes and sensory involvement in the face) but were concerned about sarcoidosis (pleocytosis) and vasculitis and so did a sural nerve biopsy.

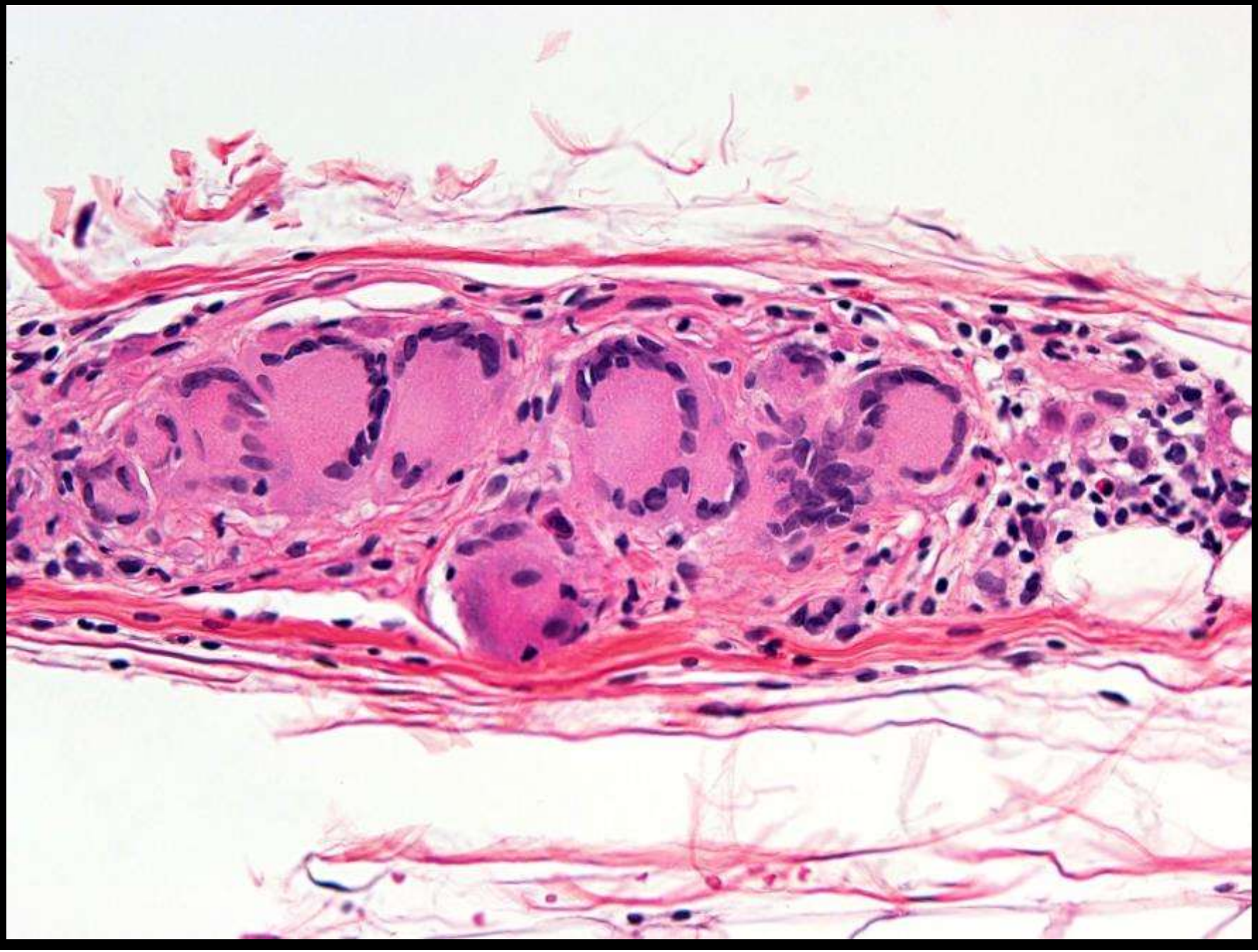
Teased Fibers – Axonal Degeneration and Some Demyelination



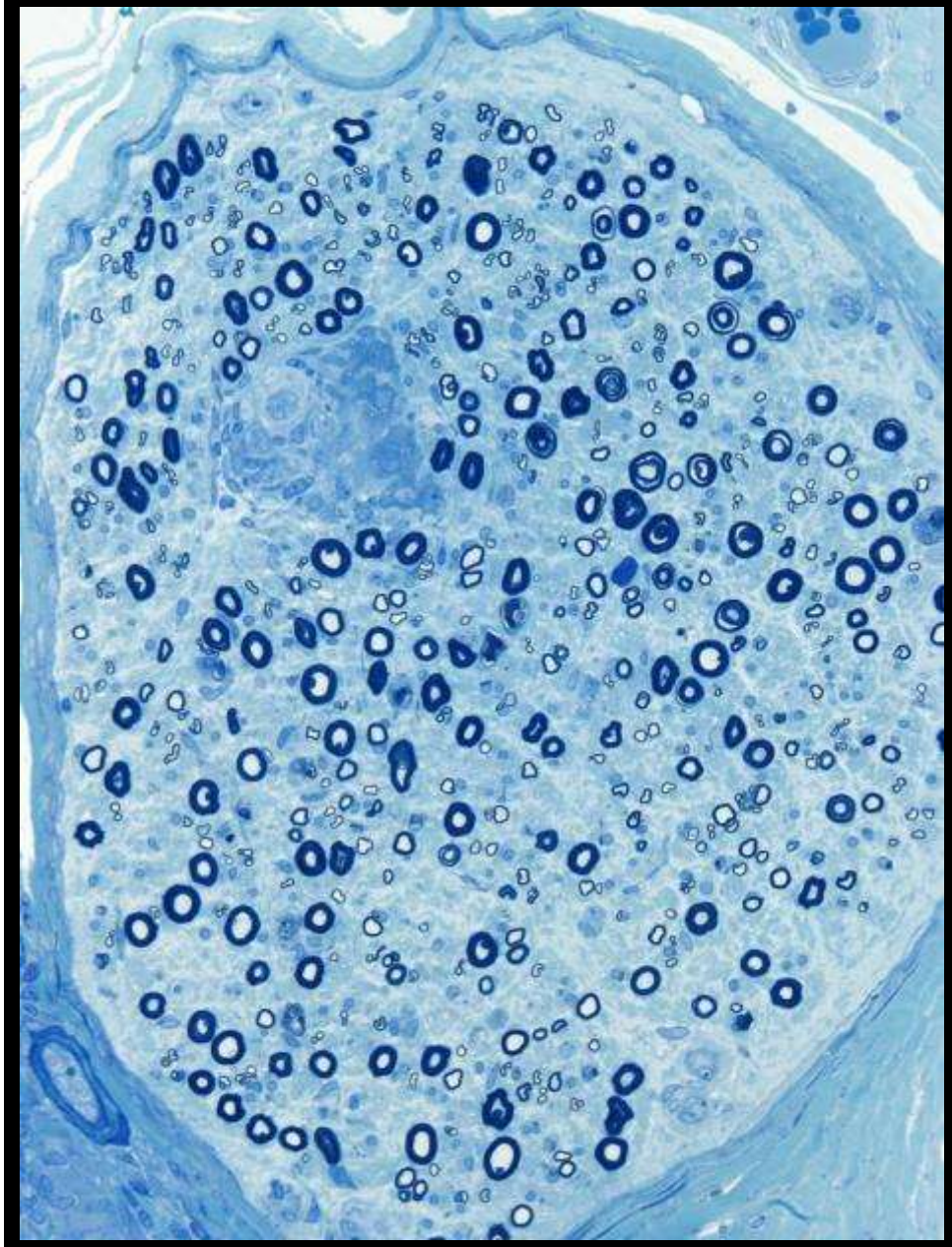
H&E – Longitudinal Section

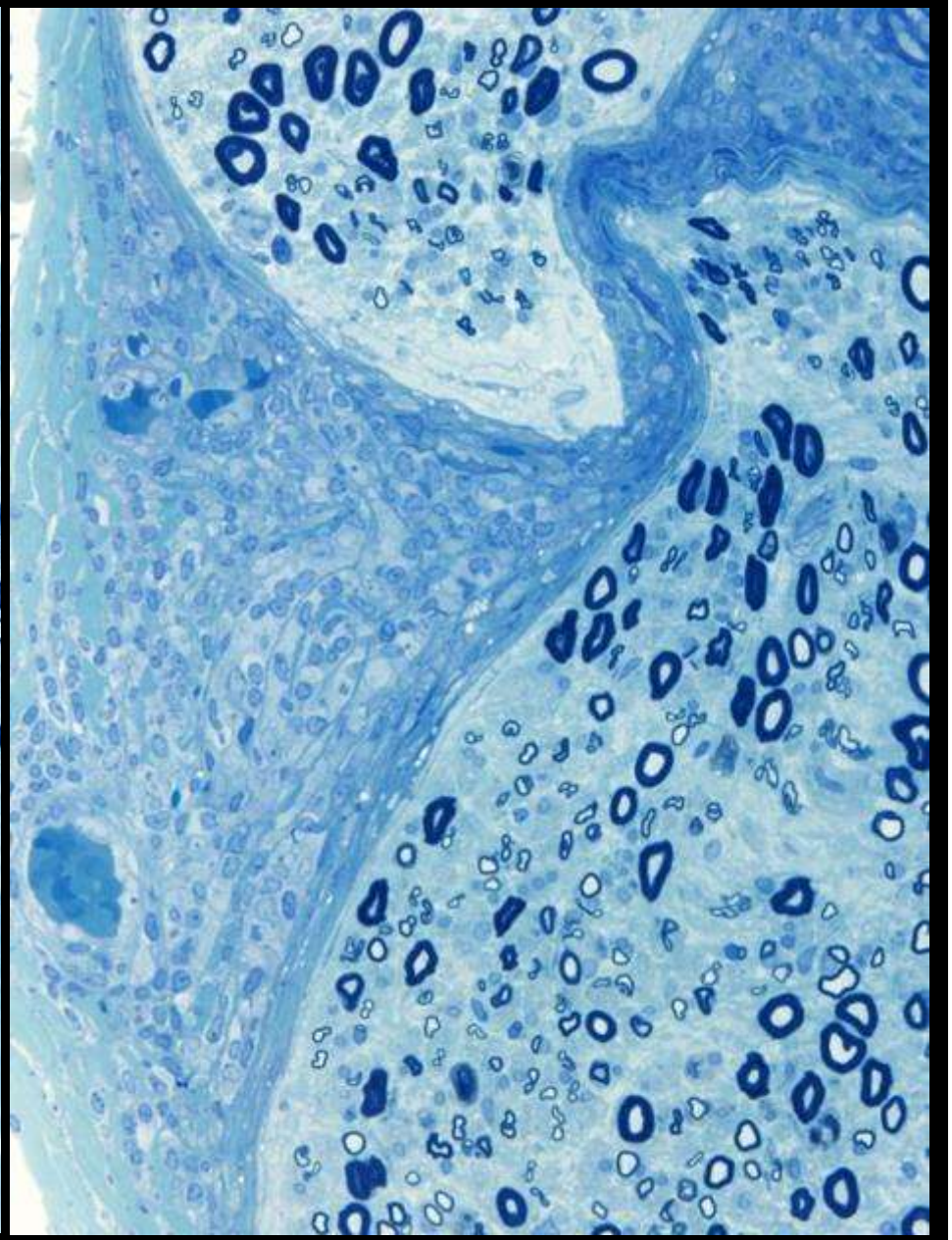


H&E – Multinucleated Giant Cells

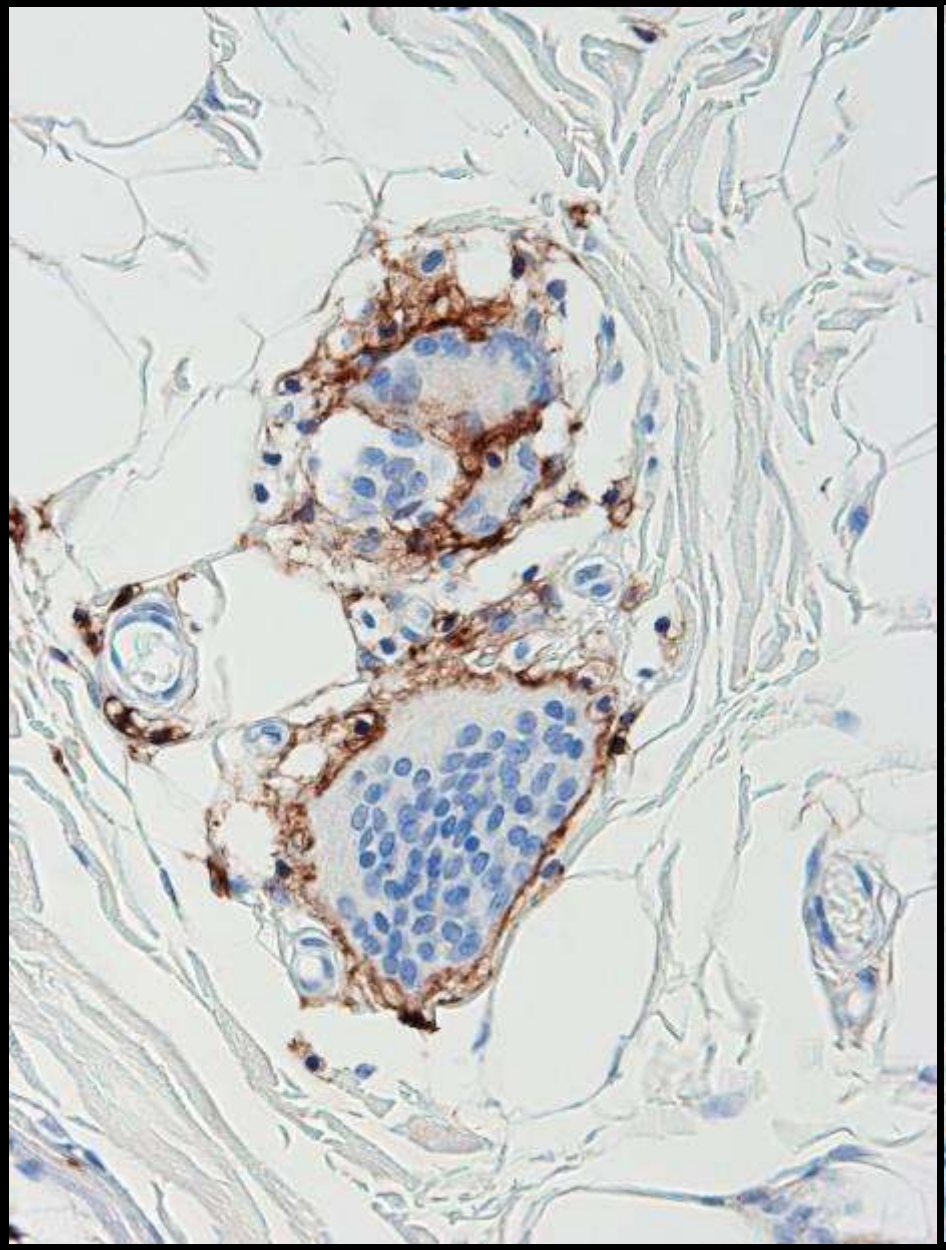


Methylene Blue – Endoneurial and Epineurial Granuloma





CD45



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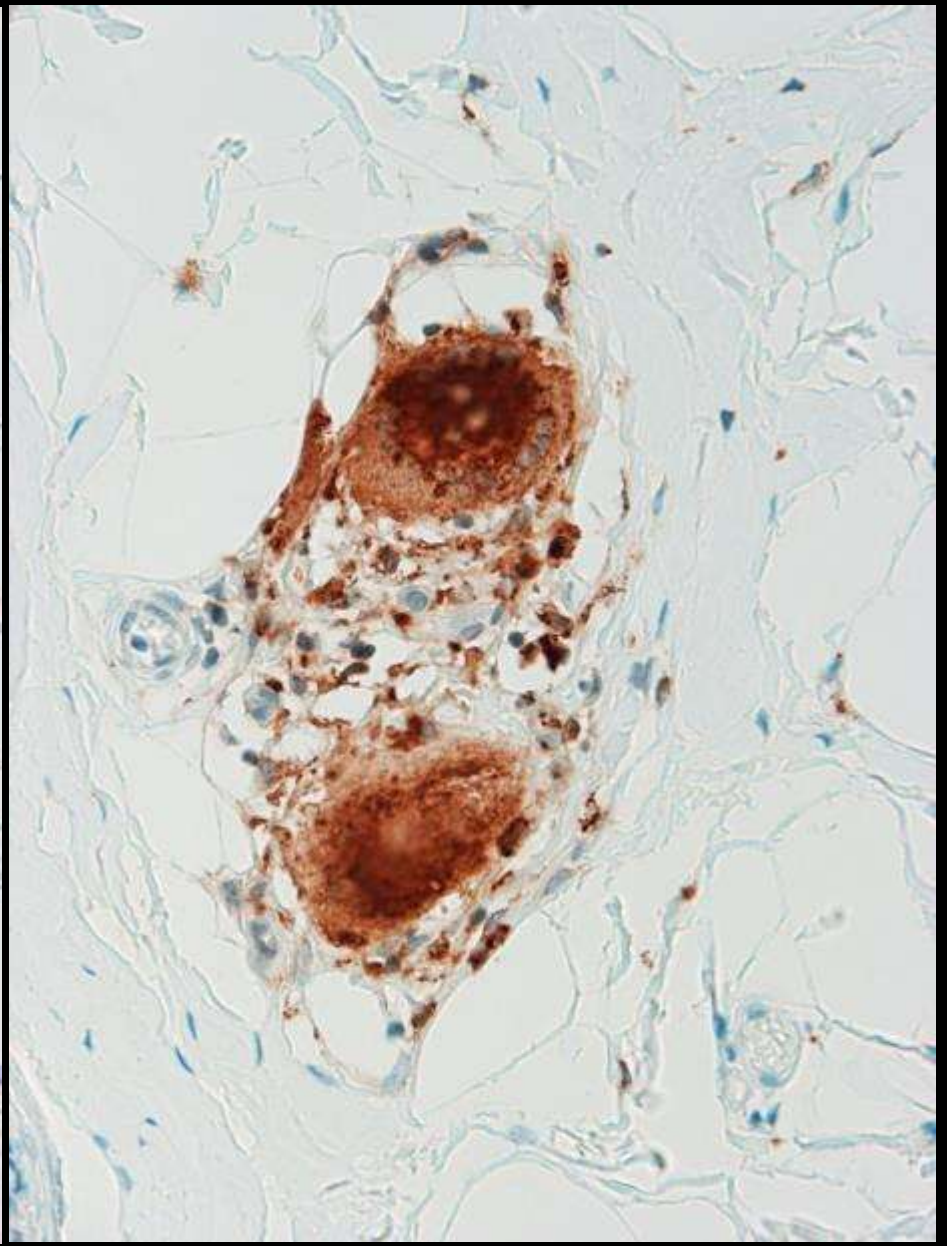


Case 4 – Outcome and Lessons

- The biopsy showed increased axonal degeneration and non-necrotic granuloma with multinucleated giant cells.
- Acid-fast stains were negative for leprosy.
- The biopsy was diagnostic of sarcoidosis.
- The patient was treated with oral prednisone and had marked improvement of numbness and ataxia.
- Without the biopsy, we would have diagnosed the patient with Sjögren's neuropathy, missed the sarcoidosis and treated less aggressively.

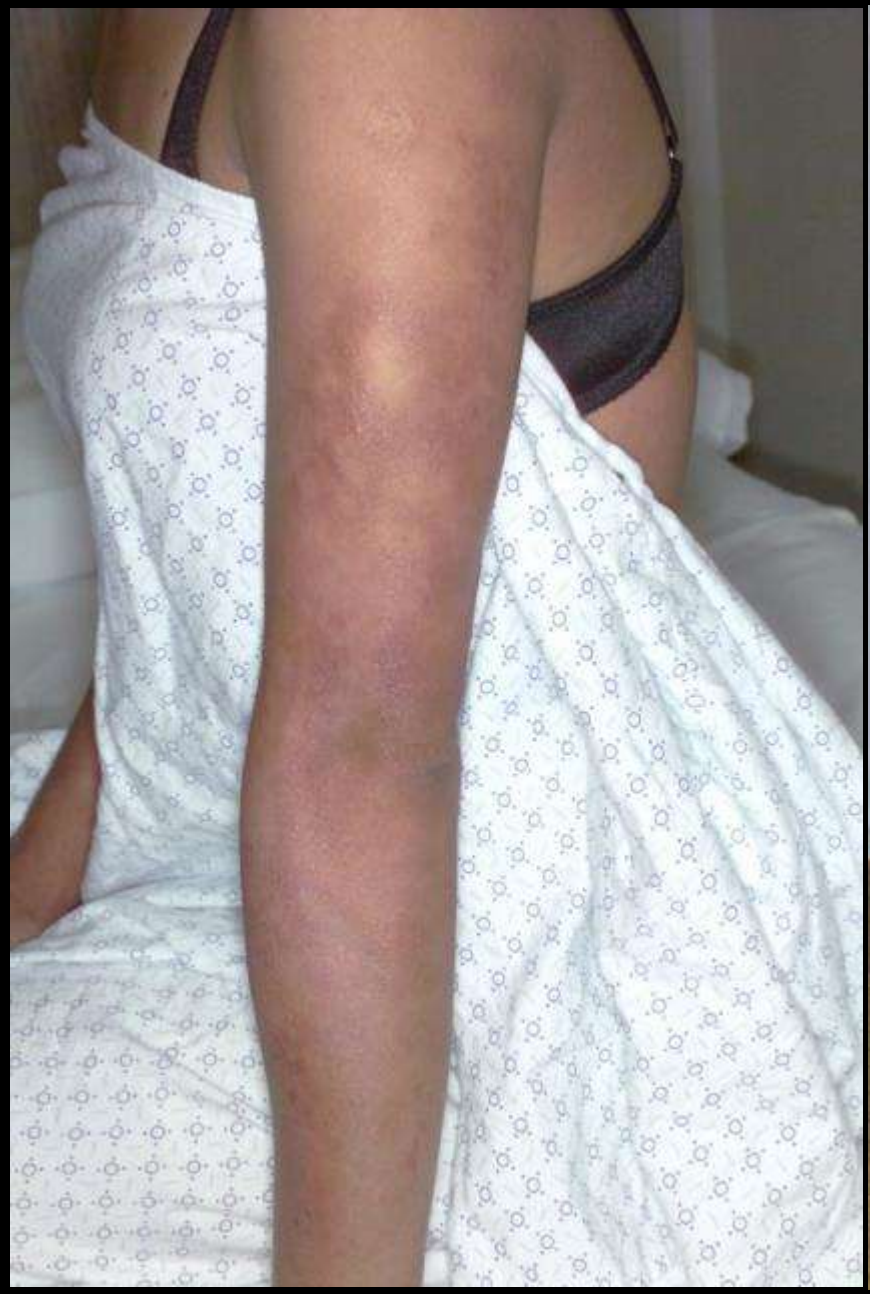
Case 5

- 27 year old woman with asymmetrical and patchy numbness.
- 1 ½ year history of burning, itching and erythema of right cheek.
- 1 year of thickening of ears, nose and lips.
- 6 months of burning and prickling numbness of lower more than upper limbs and patches of skin discoloration and erythema.
- Fevers, chills and night sweats.
- Moved to USA from Indonesia 3 years earlier.

Neurological Examination

- CN: Reduced sensation over ear pinnae and right zygomatic arch; thickened facial features.
- Motor, reflexes and gait: Normal
- Sensory: In fingers and toes she has loss of touch, pin, vibration and joint position sense. Tinnel's sign with palpation of median nerve.
- Skin: Reddish brown indurated plaques on forehead, nose and cheeks. Erythema of hands and feet.

Skin Changes



NERVE CONDUCTIONS

* = Repetitive Stim. NR = No Response.

Stimulate	(Record)	AMPLITUDE (milli/micro)volts right	left	normal	VELOCITY meters/sec. right	left	normal	DISTAL LATENCY milliseconds right	left	normal	F-WAVE LATENCY milliseconds right	left
Median, motor	(Abductor pollicis br)	-	6.6	(>4.0)	-	49	(>48)	-	4.5	(<4.5)		- 27.8
Median, sensory	(Index)	-	8	(>15)	-	49	(>56)	-	4.4	(<3.6)		-
Ulnar, motor	(Abductor digiti mini)	-	4.6	(>6.0)	-	50	(>51)	-	3.6	(<3.6)		-
Ulnar, sensory	(Fifth)	-	5	(>10)	-		(>54)	-	4.3	(<3.1)		-
Peroneal, motor	(Extensor digitorum b)	-	0.2	(>2.0)	-	42	(>41)	-	6.1	(<6.6)		-
Sural, sensory	(Ankle)	-	0	(>6)	-		(>40)	-	NR	(<4.5)		-
Tibial, motor	(Abductor hallucis)	-	0.2	(>4.0)	-	41	(>40)	-	4.8	(<6.1)		- 54.8

BLINK REFLEX

		IPSILATERAL R1	IPSILATERAL R2	CONTRALATERAL R2
L. Trigeminal Supraorbital	(Orbic. Oculi)	10.4 (8-13)	33.2 (29-41)	35.5 (29-44)

VOLUNTARY MOTOR UNIT POTENTIALS

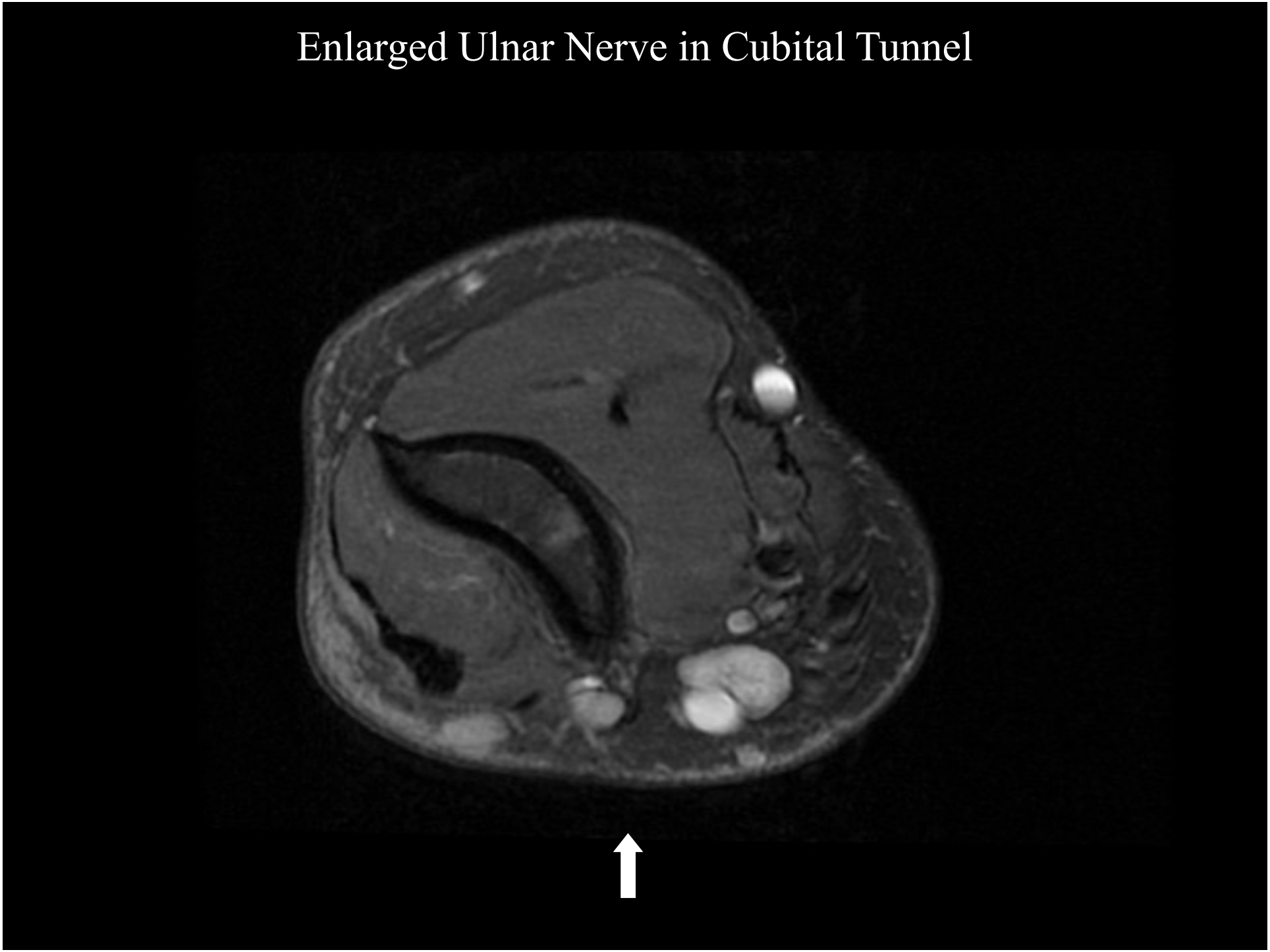
MUSCLE	INSERT. ACTIVITY	SPONTANEOUS Fib.	Fasc.	MUP NORMAL	RECRUITMENT Act.	Reduced	Rapid	DURATION LONG	SHORT	AMPLITUDE HIGH	LOW	PHASES %
TURNS												
L. First dorsal interosseous	Normal	0	0					+		+		
L. Abductor hallucis	Increased	++	0									
L. Biceps brachii	Normal	0	0	Normal								
L. Medial gastroc.	Normal	0	0					++		++		
L. Tibialis anterior	Normal	0	0					+		+		
L. Vastus medialis	Normal	0	0	Normal								

Interpretation: There is electrophysiologic evidence of an axonal length-dependent sensorimotor peripheral neuropathy.

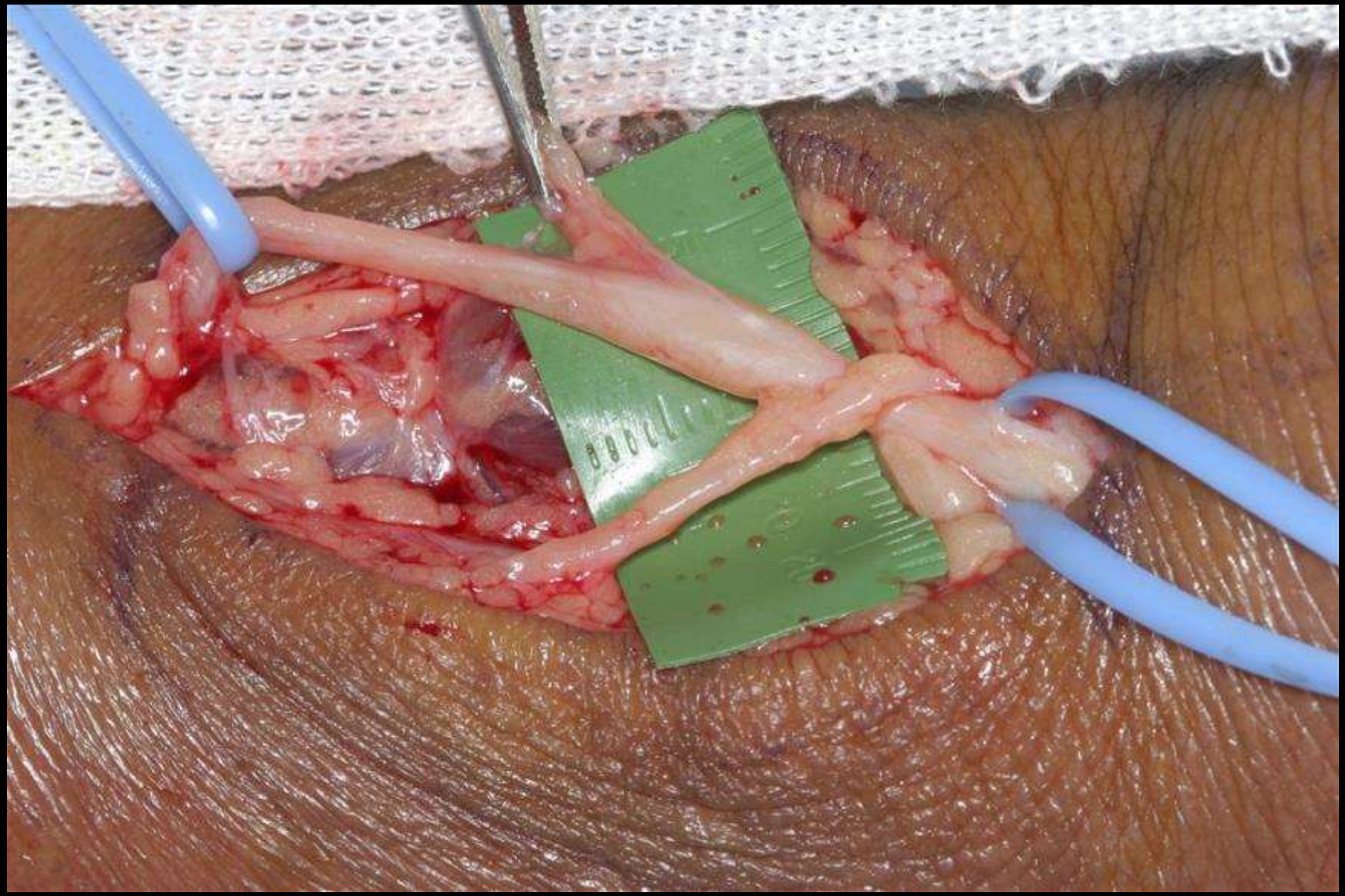
Evaluation

- QST showed decreased vibration, cooling and heat pain sensation in feet.
- Thermoregulatory sweat test showed global anhidrosis of 98% of body surface.
- MRI: Marked enlargement of the ulnar nerve especially in cubital tunnel with enlargement of nerve fascicles and bundles with intense gadolinium enhancement.

Enlarged Ulnar Nerve in Cubital Tunnel

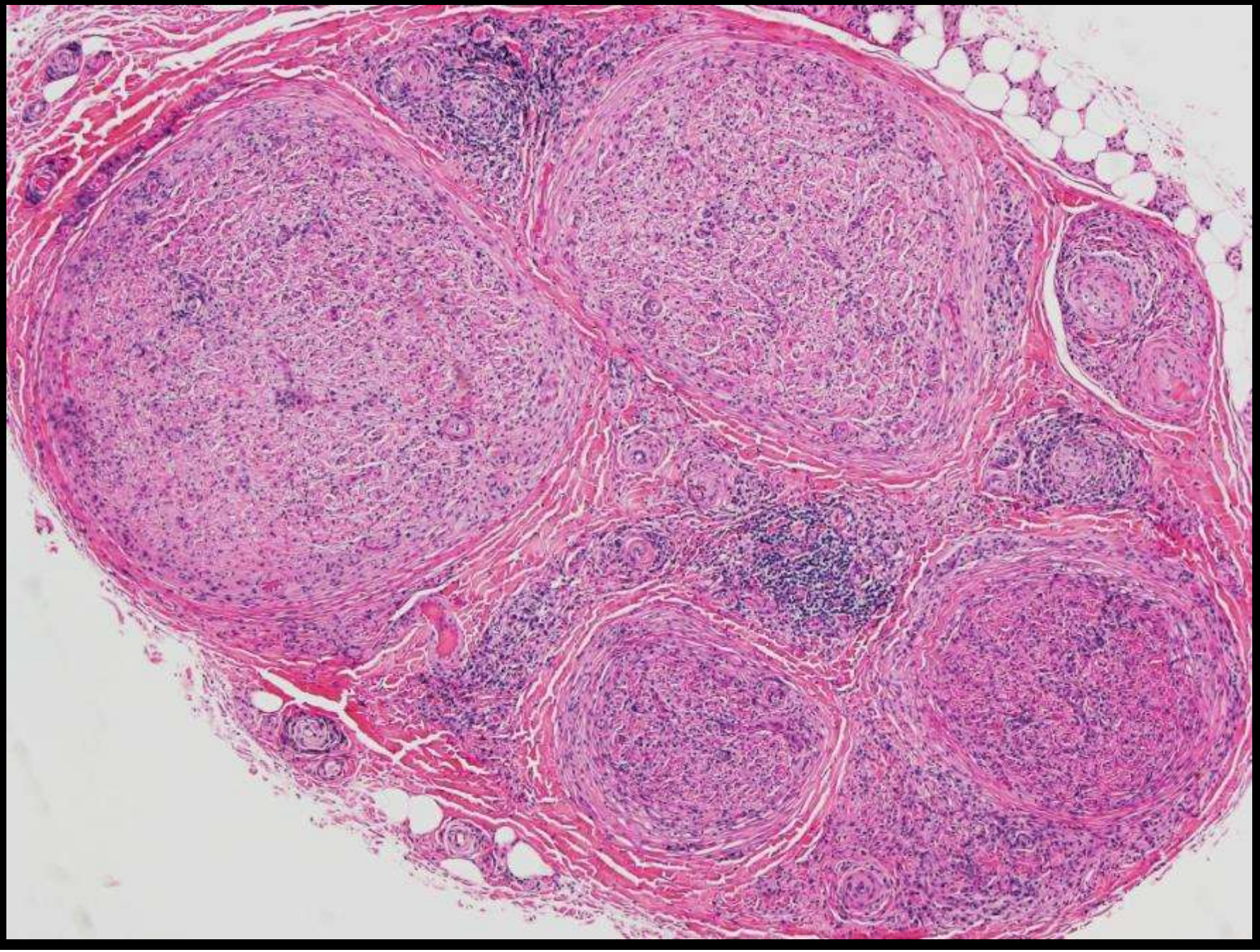


Sural Nerve Biopsy – Enlarged Nerve

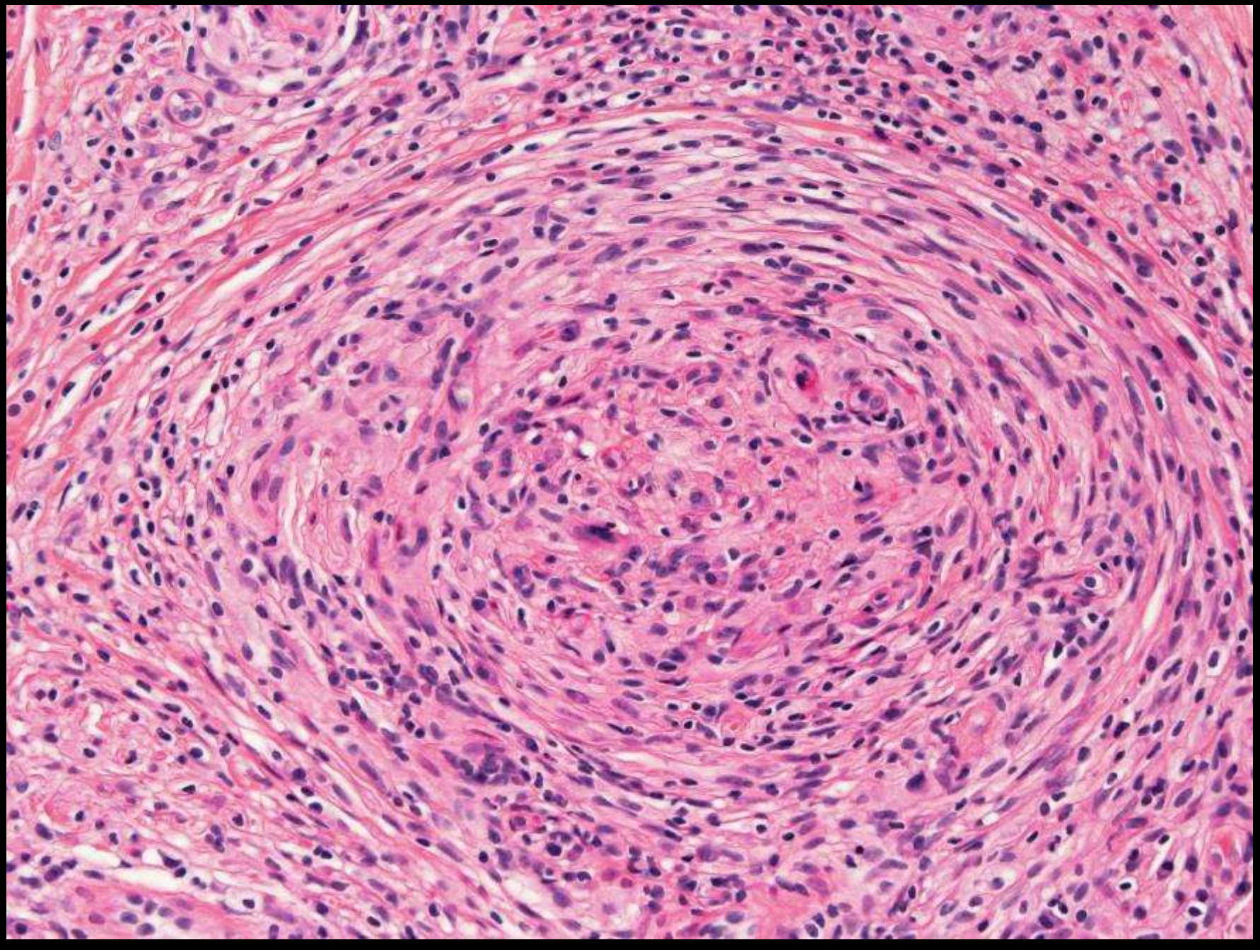


Teased Fibers – Axonal Degeneration and Demyelination

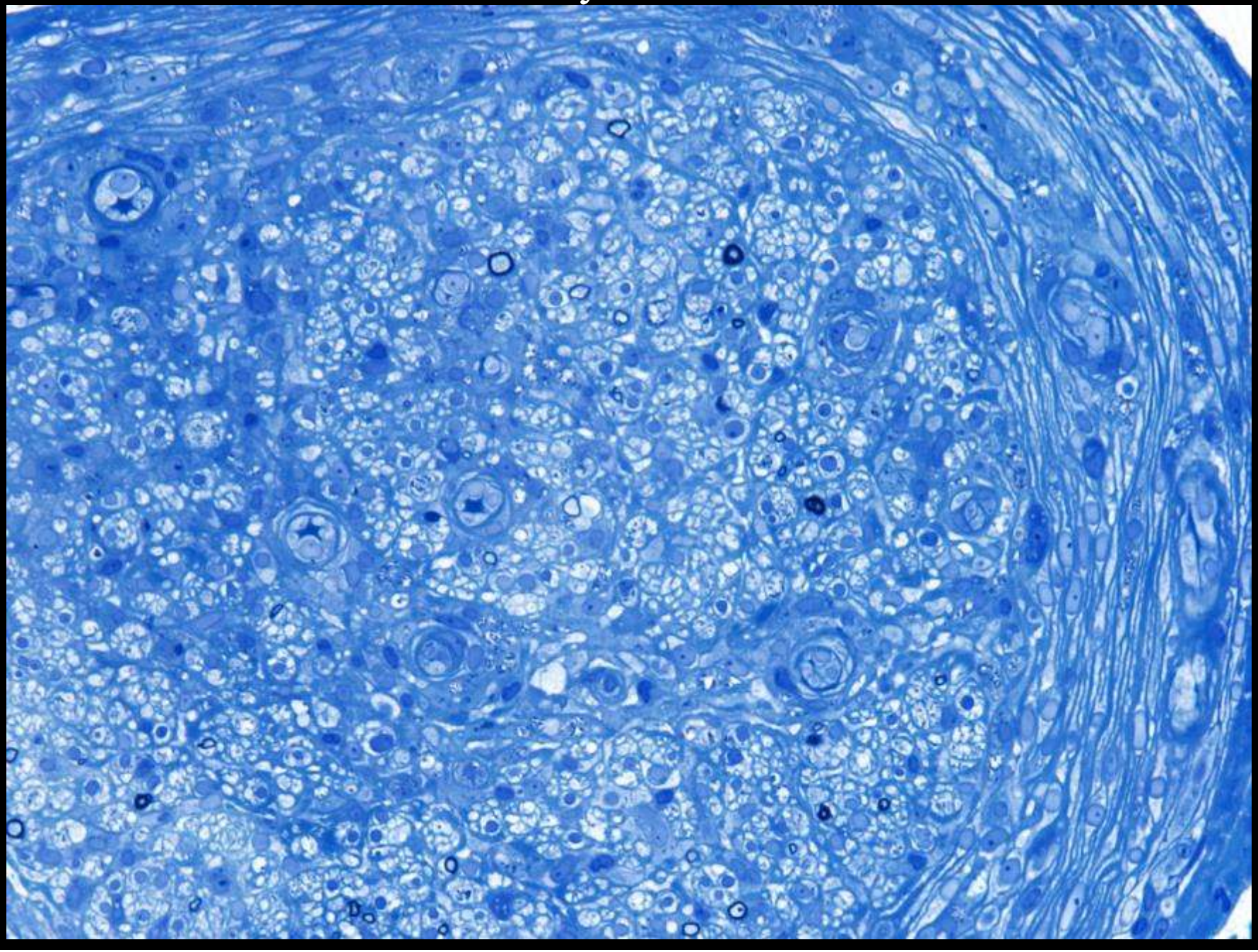
H&E



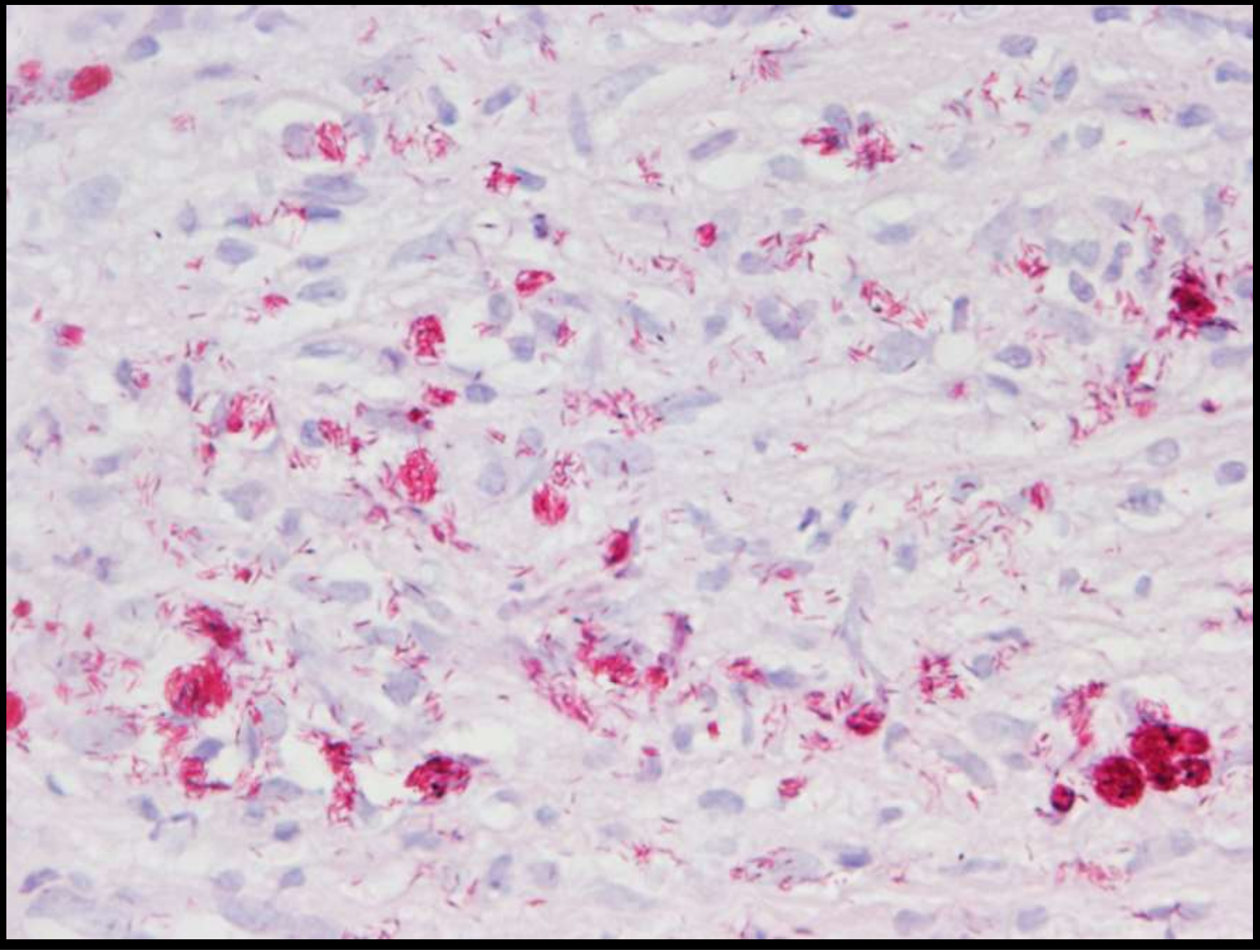
H&E



Methylene Blue



Fite Positive for Acid-Fast Bacilli



Case 5
Pathological Diagnosis and Outcome

- Diagnosis: Lepromatous Leprosy
- Outcome: Treated with Dapsone, Rifampin and minocycline.
  - She had decreased erythema and swelling.
  - By 10 months her numbness was much better as her EMG and sweat test were improved.

Case 6

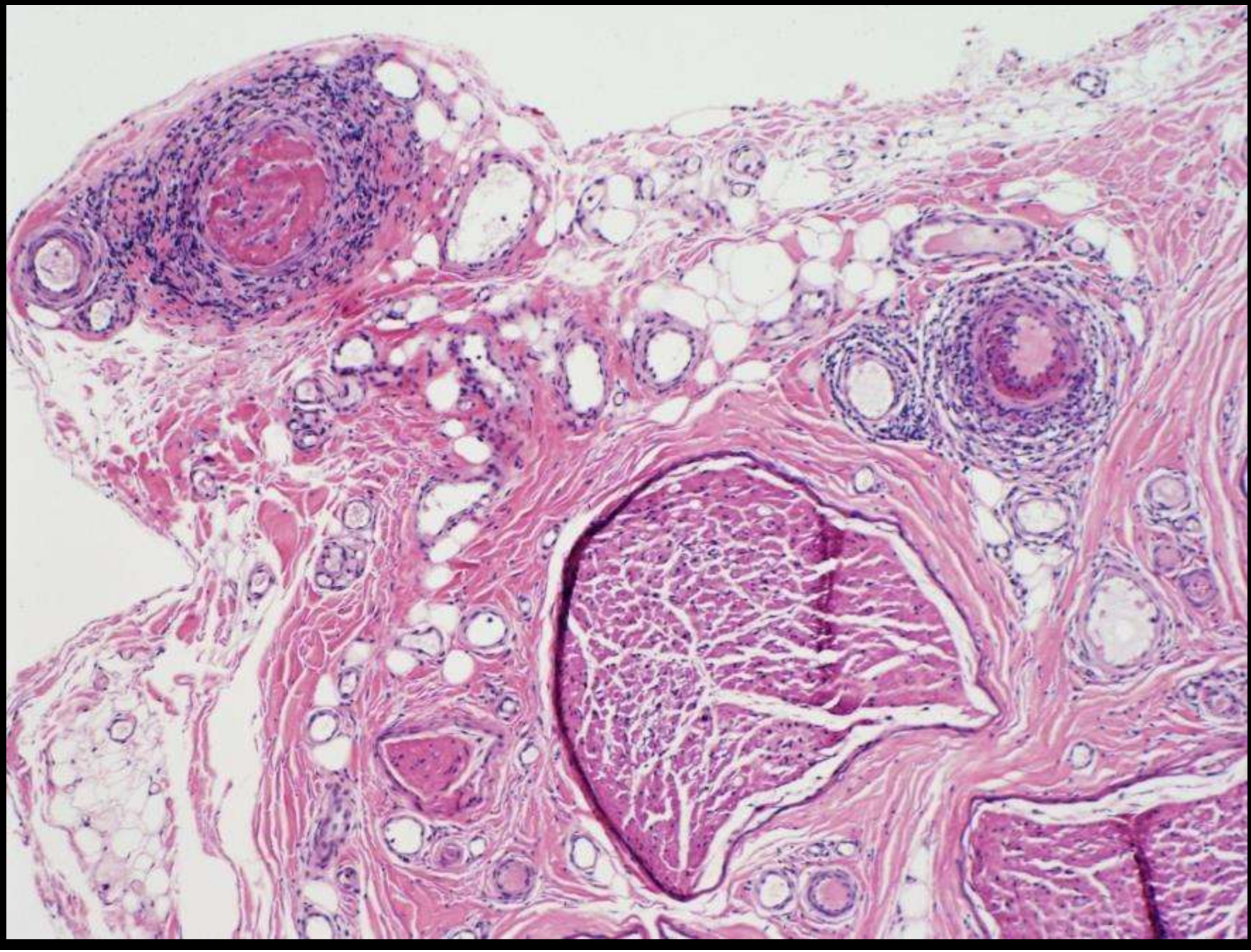
- 17 year old girl with acne on Minocycline developed acute left arm pain, weakness and numbness (lateral two fingers).
- 11 days later, she developed asymmetrical lower limb pain and numbness of her thighs and feet.
- Neurological examination showed left arm and bilateral ankle dorsiflexion weakness and reduced sensation in left hand and both feet.

Evaluation

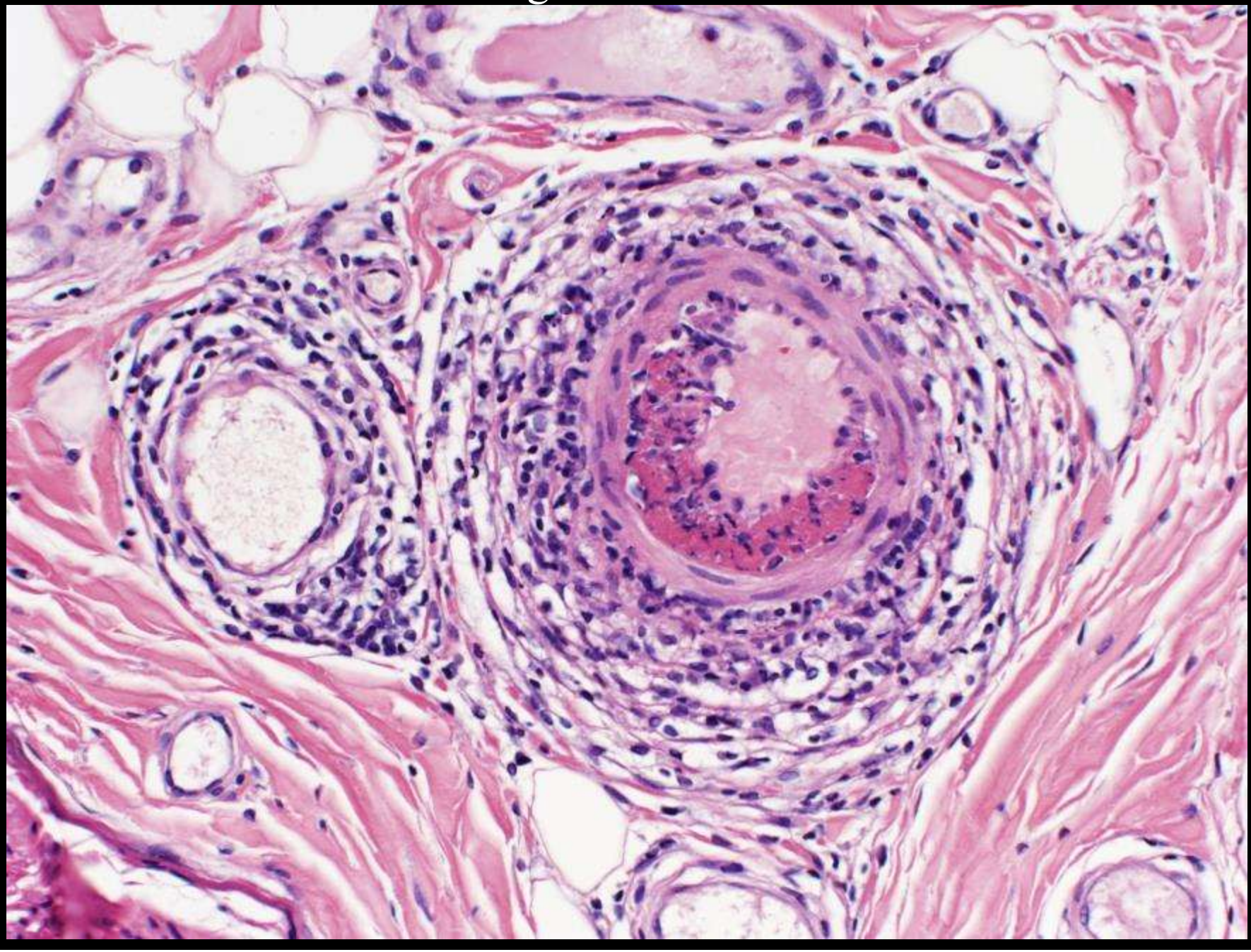
- NCS/EMG showed a subacute neurogenic disorder that would localize to the brachial plexus or multiple upper limb peripheral nerves (multiple mononeuropathy).
- MRI of brachial plexus showed generalized increased T2 signal.
- ANA was positive (1:160; 2.0), CRP was elevated at 28.4 mg/L (<3.0).
- A left superficial radial nerve biopsy was performed.

Teased Fibers – Acute Axonal Degeneration

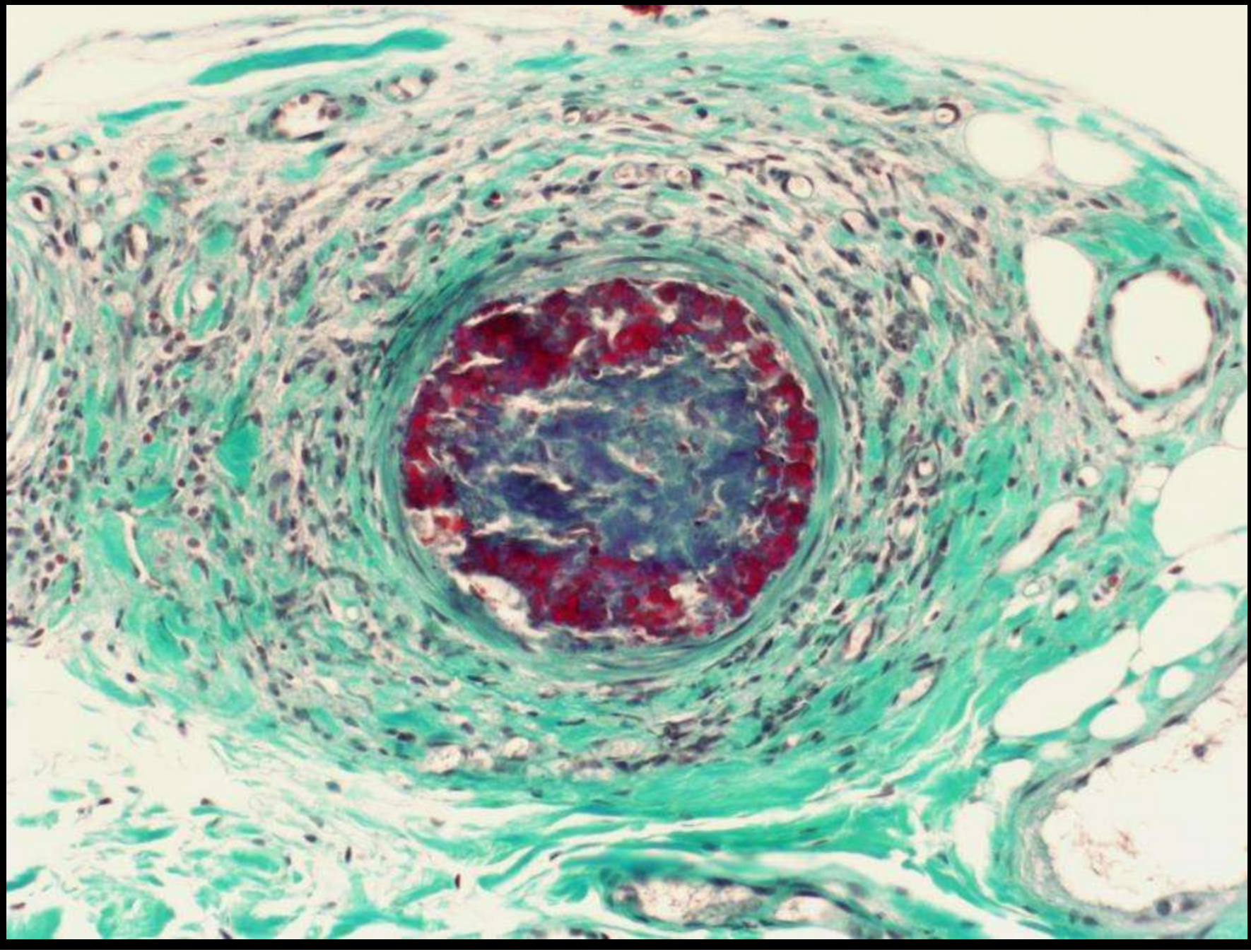
H&E



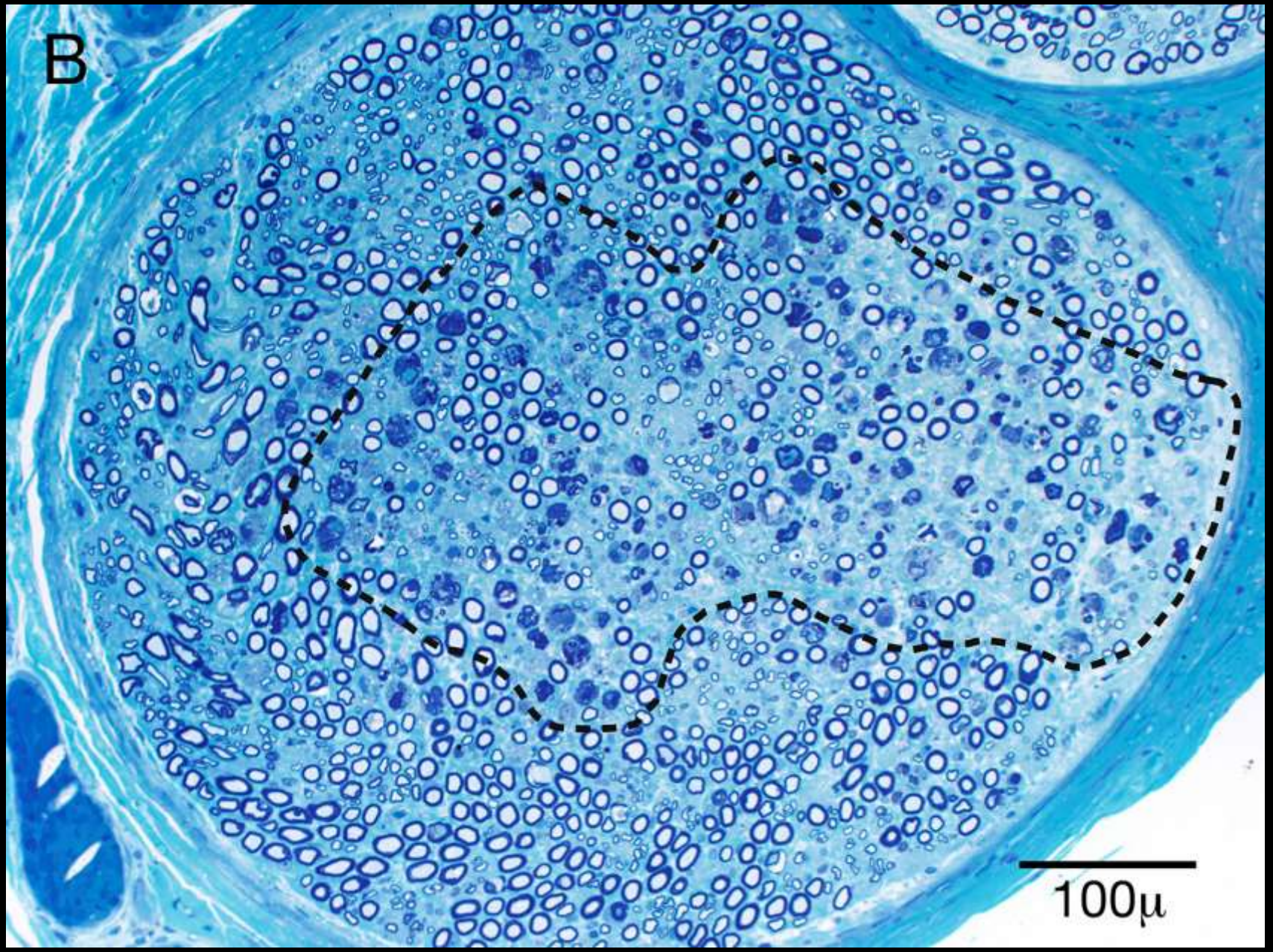
H&E – Large Arteriole Vasculitis



Trichrome – Fibrinoid Necrosis



Methylene Blue – Central Fascicular MF Degeneration



Case 6
Pathological Diagnosis and Outcome

- Diagnosis of nerve large arteriole necrotizing vasculitis likely induced by minocycline.
- Minocycline was discontinued and the patient was treated with IV methylprednisolone and she had improvement of pain and weakness.
- The biopsy lead to diagnosis and treatment for vasculitis.
- Three cases of vasculitic neuropathy associated with minocycline use have recently been described.

Baratta JM, Dyck PJB, Brand P, Thaisetthawatkul P, Dyck PJ, Engelstad JK,Goodman B, Karam C. Vasculitic neuropathy following exposure to minocycline.Neurol Neuroimmunol Neuroinflamm. 2015 Nov 12;3(1).

Targeted Fascicular Nerve Biopsy

- Many neuropathies are not well evaluated by distal cutaneous nerve biopsies.
  - motor neuropathies
  - focal neuropathies
  - proximal neuropathies (plexopathies and polyradiculopathies)
- There is a need to biopsy other nerves than distal cutaneous nerve.
- To meet this need, we have developed a multidisciplinary practice of targeted fascicular nerve biopsies.

Background

Proximal nerve biopsies have been generally avoided.

- Potential danger of causing new weakness
- Difficulty in selecting an appropriate biopsy site (pathological lesion)

In the past, we have occasionally performed proximal fascicular biopsies in patients with:

- Focal nerve conduction block (MMN)
- Palpable nerve masses
- Imaging abnormalities

Background

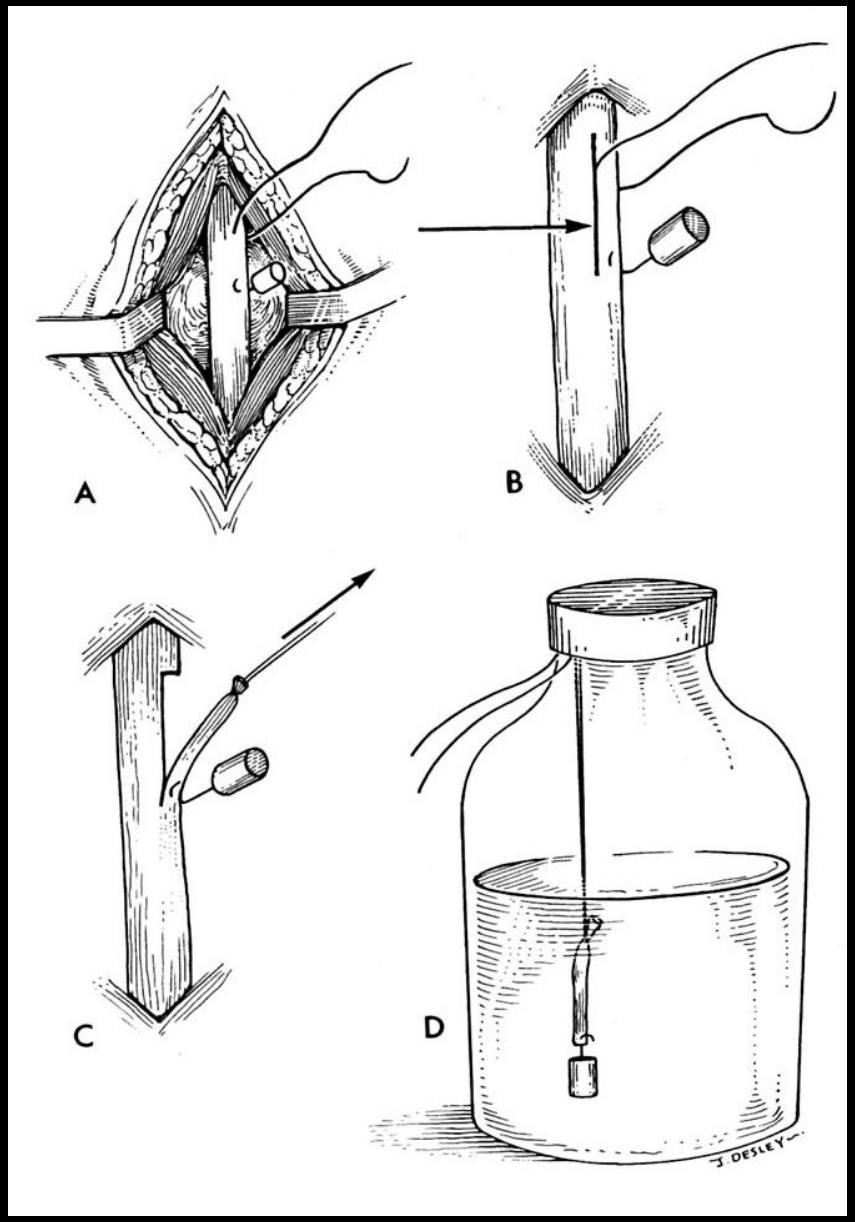
- Previously, MRI did not resolve peripheral nerves well enough to be as clinically useful as desirable.
- With higher power magnets (3 Tesla), and radiologists with special interest in nerve, the role of MRI in characterization and diagnosis of PNS lesions is improving.

Targeted Fascicular Nerve Biopsy

Objective

- To study the use of targeted fascicular nerve biopsies from proximal nerves with focal MRI abnormality.
- To compare the yield:
  - whole distal cutaneous biopsies (usual approach)
  - targeted fascicular nerve biopsies from MRI lesions (new approach)

Surgical Technique of Fascicular Nerve Biopsy



From: Dyck and Lofgren, Mayo Clinic Proceedings, 1966

Methods

To study proximal fascicular nerve biopsy from MRI lesions, the following conditions should be fulfilled:

- a peripheral nerve neurologist to select and evaluate appropriate cases
- a peripheral nerve radiologist with a high resolution MRI scanner (3 T)
- a peripheral nerve surgeon to perform targeted nerve biopsies
- a peripheral nerve pathologist with specialization in processing and interpreting nerve biopsies

Clinical Methods

- We identified patients with a focal or asymmetric neuropathy and MRI lesion(s) of roots, plexus or proximal limb nerves.

- Patients underwent nerve biopsy:
  - whole distal cutaneous
  - fascicular proximal (usually mixed motor and sensory)
  - both

Clinical Results

- 138 patients with abnormal MRI of the nerve
- Mean age 48.8 years (range 3 - 77 years)
- 68 males and 70 females
- 12 children and 126 adults

Clinical Neuropathy Patterns (n=138)

- 59 Mononeuropathies:
  38 sciatic, 8 ulnar, 5 median, 4 radial, 2 femoral, 2 tibial
- 39 Brachial plexus neuropathies
- 29 Polyradiculopathies/polyradiculoneuropathies:
  12 asymmetric sensorimotor
  7 symmetric sensorimotor
  6 purely sensory
  4 cauda equina syndrome
- 12 Lumbosacral radiculoplexus neuropathies
- 6 Cranial neuropathies
- 1 Multiple mononeuropathy
- 8 patients had more than one of these types

MRI Results

- All 138 cases had abnormal MRI of nerve.
- Usually MRI did not differentiate among pathologies but identified the nerve lesion.
- The MRI lesions often involved more than one nerve segment (root, plexus or nerve).

Nerve Biopsy Results (n=138)

- 30 whole distal cutaneous nerve biopsies
  - 24 sural, 5 superficial peroneal, 1 superficial radial
- 130 patients had proximal nerve biopsies
  - 65 fascicular mixed motor and sensory nerves
    42 sciatic, 9 median, 7 ulnar, 2 peroneal,
    3 femoral, 2 radial, 1 tibial
    (1 patient had both median and ulnar)
  - 35 fascicular brachial plexus
  - 28 lumbar rootlet
  - 1 whole proximal cutaneous (great auricular)
  - 1 fascicular cranial (facial)

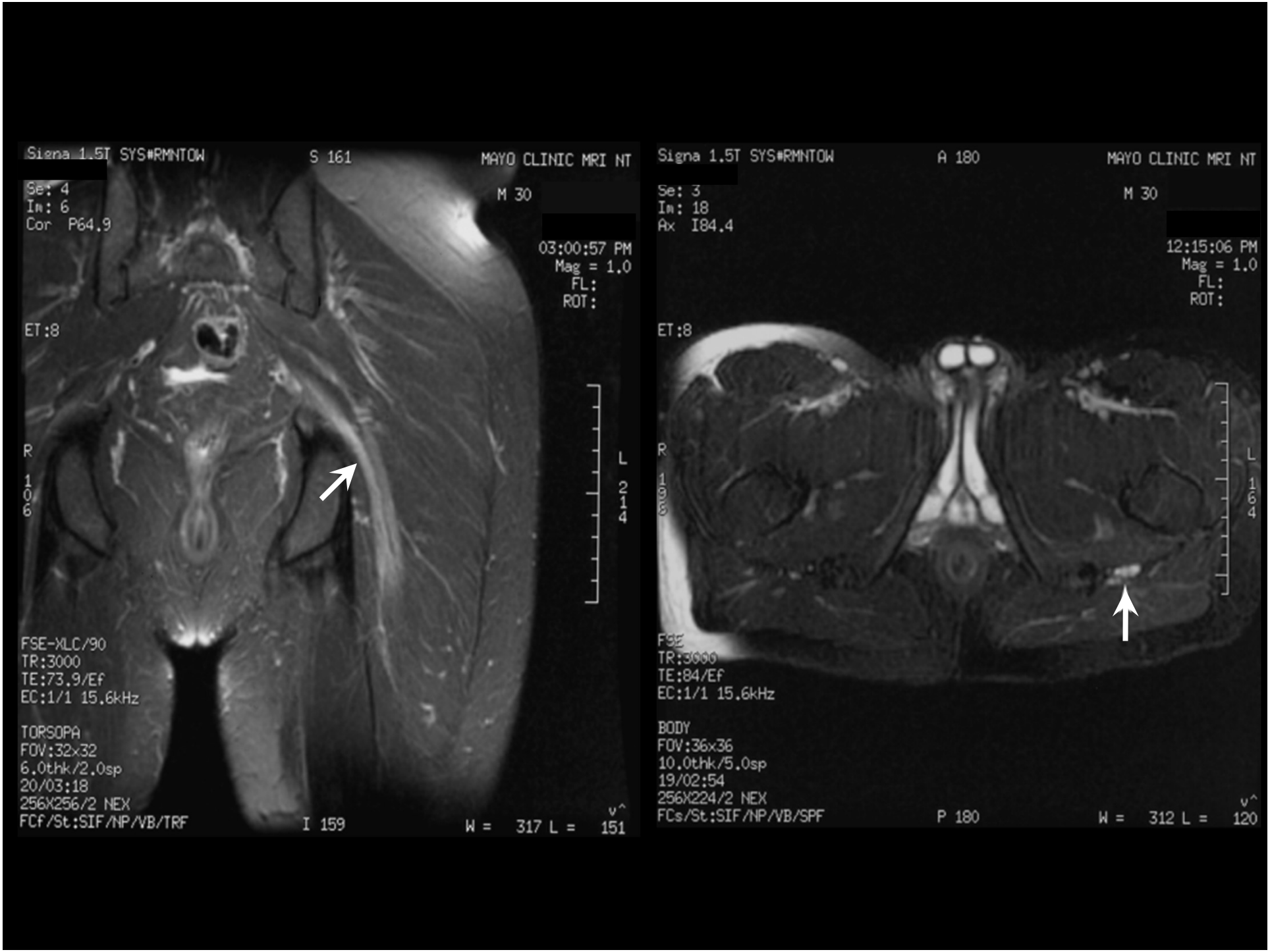
Nerve Biopsy Results

- Nerves biopsied:
  - 108 had only proximal biopsy
  - 8 had only whole distal cutaneous biopsy
  - 22 had both proximal and distal biopsies
- In general, a proximal fascicular biopsy was performed when the distal biopsy was non-diagnostic.

Examples of Targeted Fascicular Nerve Biopsies from MRI Lesions

Case 7

- 30 year old man with left foot drop and pain over 2 years. Hx of Hodgkin's disease 19 years earlier.
- Neurological examination and EMG showed left sciatic neuropathy.
- MRI showed increased T_2 signal and thickening of left proximal sciatic nerve and the L5 and S1 nerve roots.
- Whole sural and then fascicular sciatic biopsies were obtained.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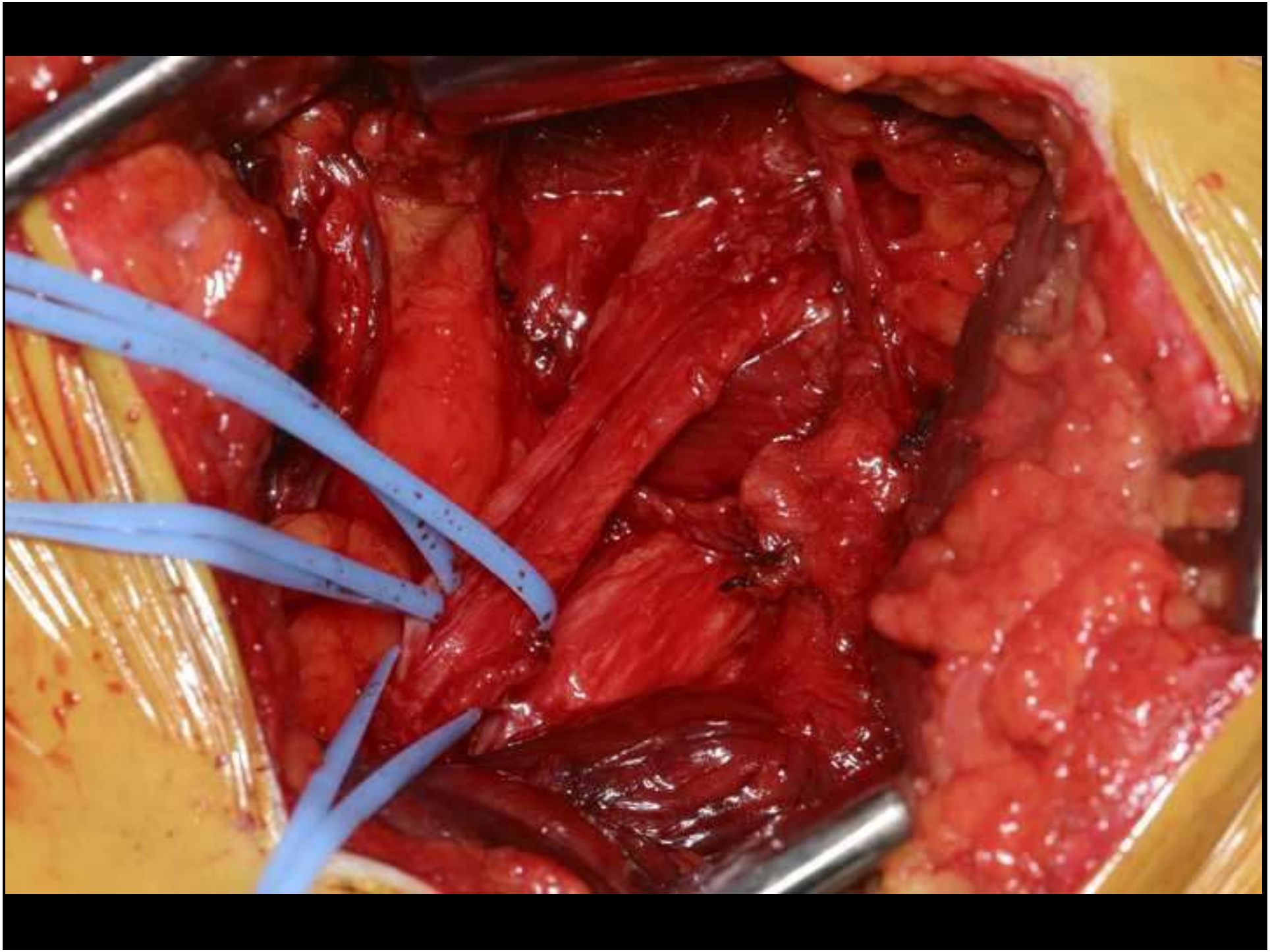
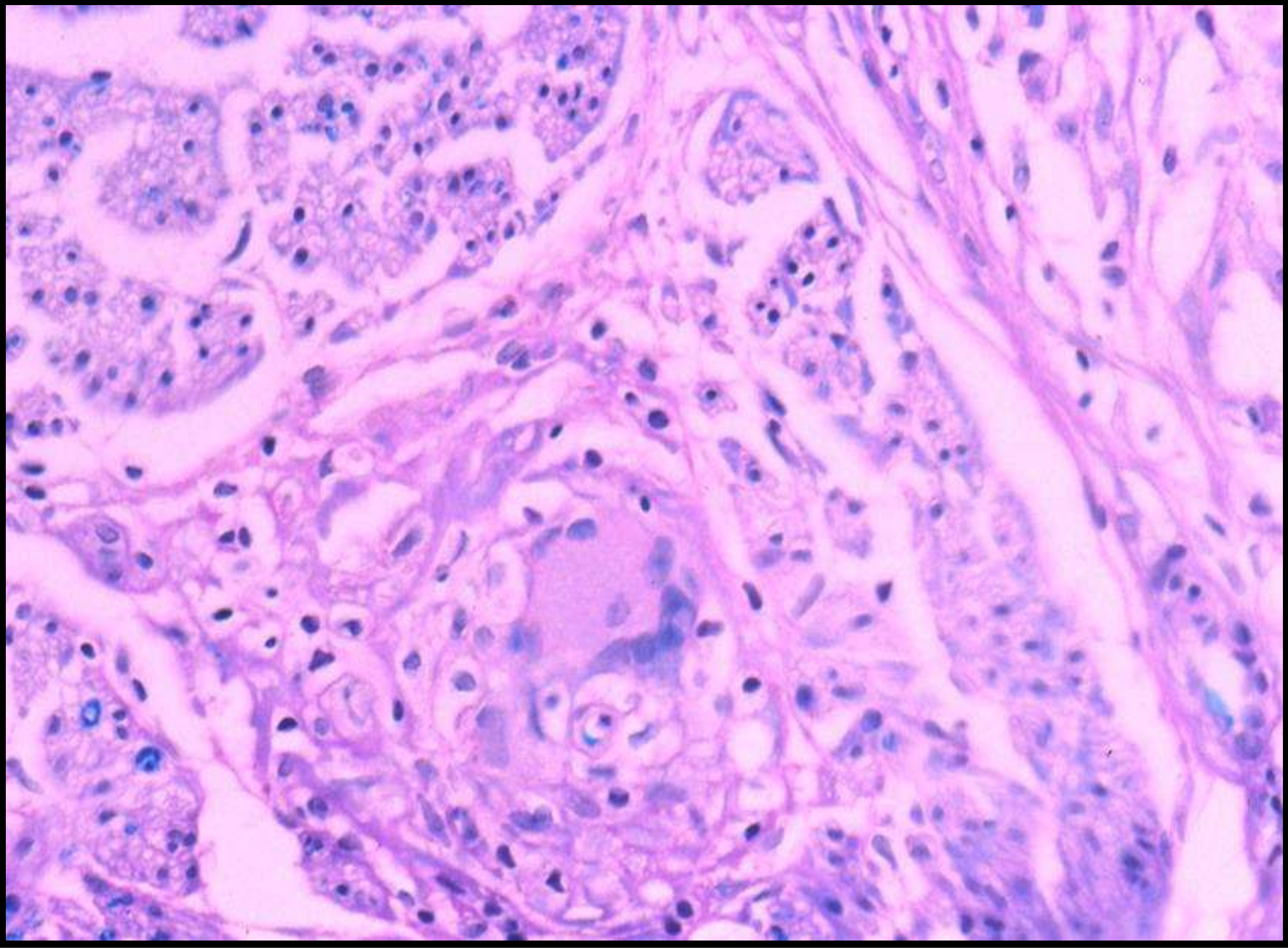
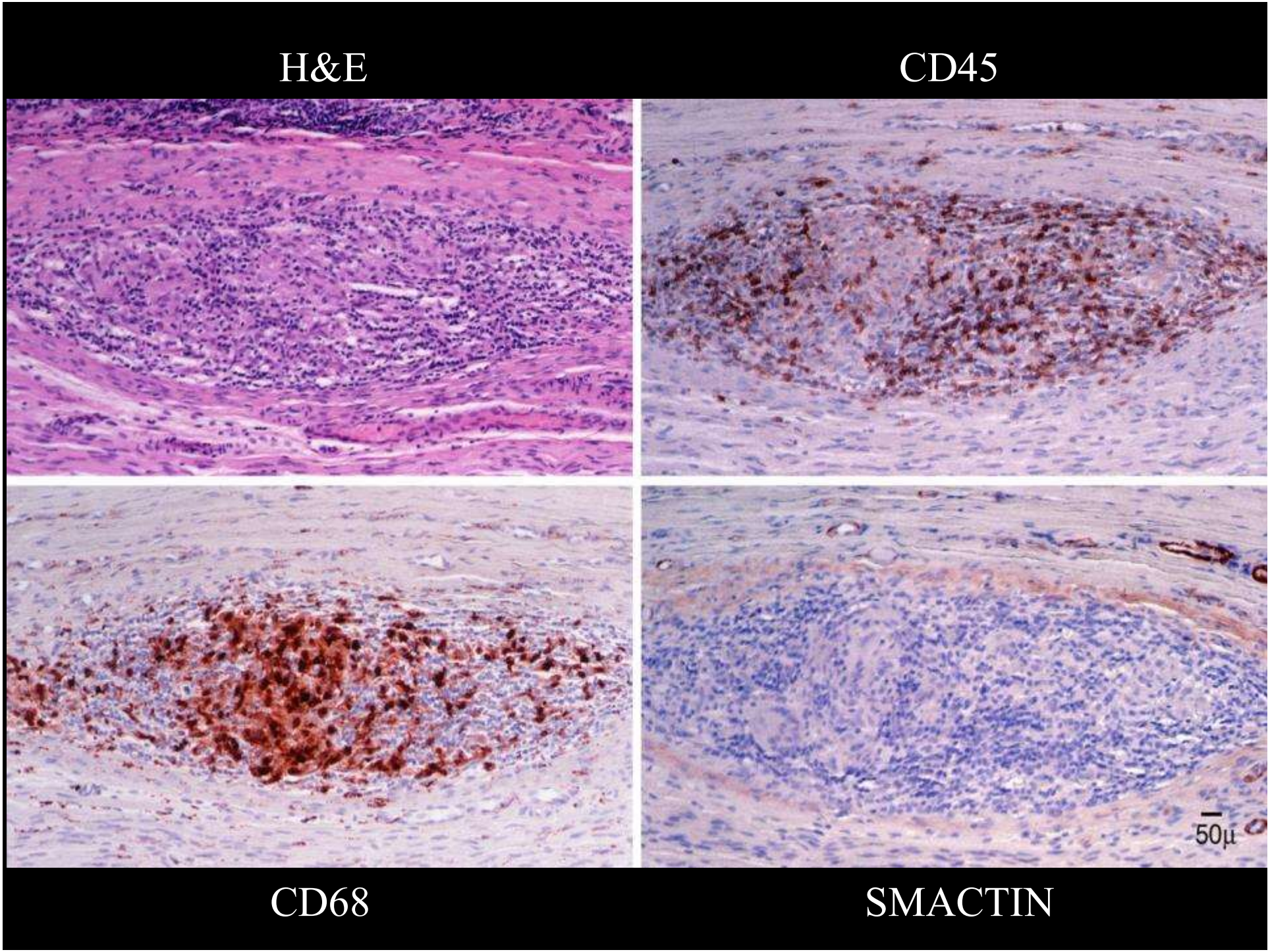


Luxol Fast Blue/PAS – Multinucleated Giant Cell

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Case 7

- Pathology: nerve granuloma
- Diagnosis: peripheral nerve sarcoidosis
- Treatment: steroids

Case 8

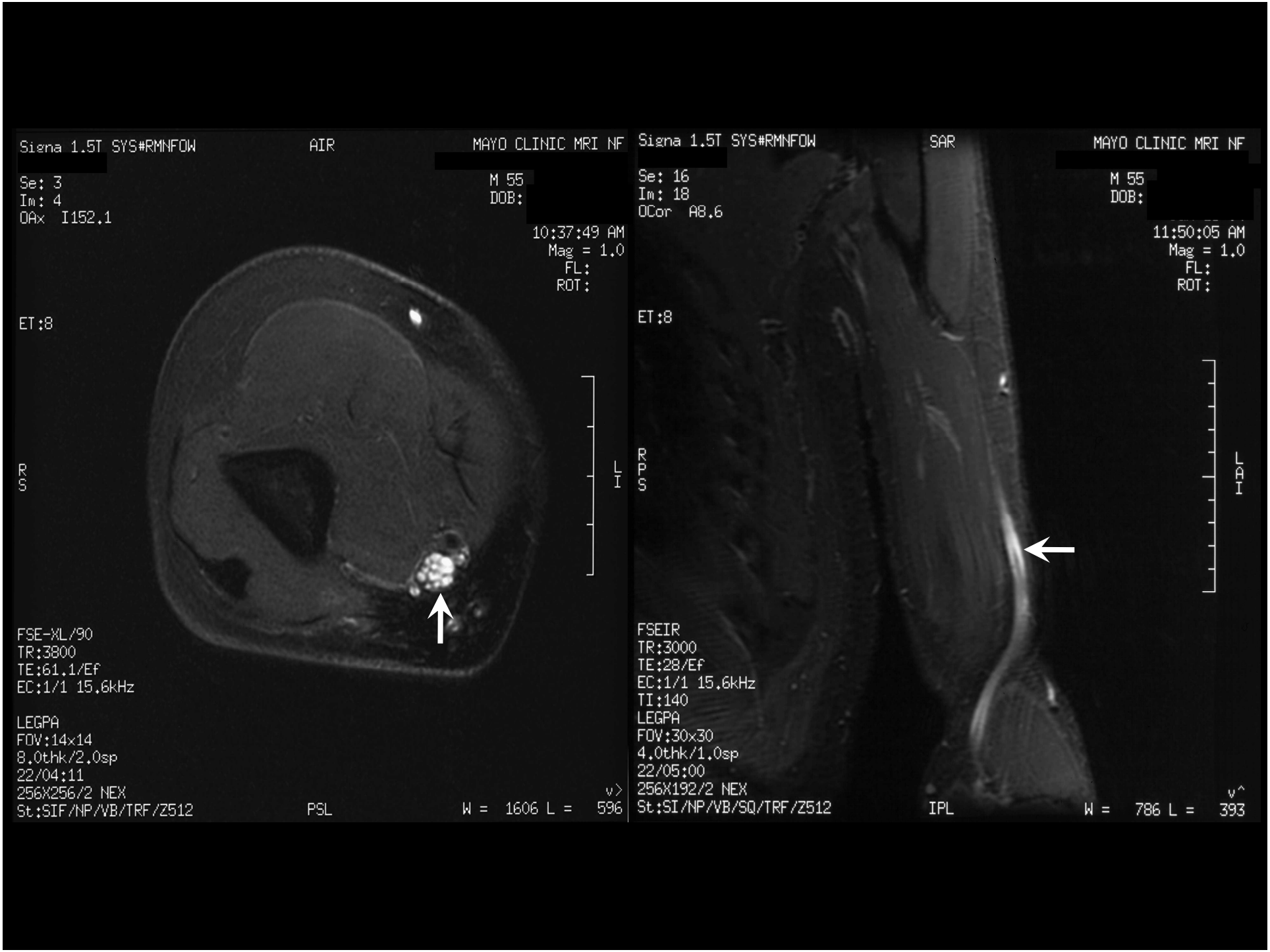
- 55 year old man with severe numbness (over 6 years) of left hand (including palm). No pain. Previous carpal tunnel release with no benefit.
- EMG showed poorly localized left median neuropathy.
- MRI showed a fusiform enlargement and increased T_2 signal of the median nerve near the elbow.
- A left fascicular median nerve biopsy at the elbow was performed.

Nerve Conduction Studies

Stimulate (Record)	A (mV/μV)	CV (m/s)	DL (ms)	F (ms)
L. Median motor (APB)	4.3 (>4)	36 (>48)	4.5 (<4.5)	35.9
L. Ulnar motor (ADM)	9.3 (>6)	53 (>51)	3.3 (<3.6)	31.9
L. Median sensory (palm)	0 (>50)		NR (<2.3)	
L. Median sensory (index)	0 (>15)		NR (<3.6)	
L. Ulnar sensory (palm)	30 (>15)	55 (>54)	2.2 (<2.3)	
R. Median sensory (palm)	55 (>50)		2.2 (<2.3)	
R. Ulnar sensory (palm)	40 (>15)		2.2 (<2.3)	

EMG

Muscle	Insertional activity	Fibrillation	Fasciculation	MUP
L. Abductor pollicis brevis	Increased	0	+	2 + big
L. Biceps brachii	Normal	0	0	Normal
L. First dorsal interosseous	Normal	0	0	Normal
L. Flexor carpi radialis	Normal	0	0	Normal
L. Flexor pollicis longus	Normal	0	0	Normal
L. Pronator teres	Normal	0	0	Normal
L. Triceps brachii	Normal	0	0	Normal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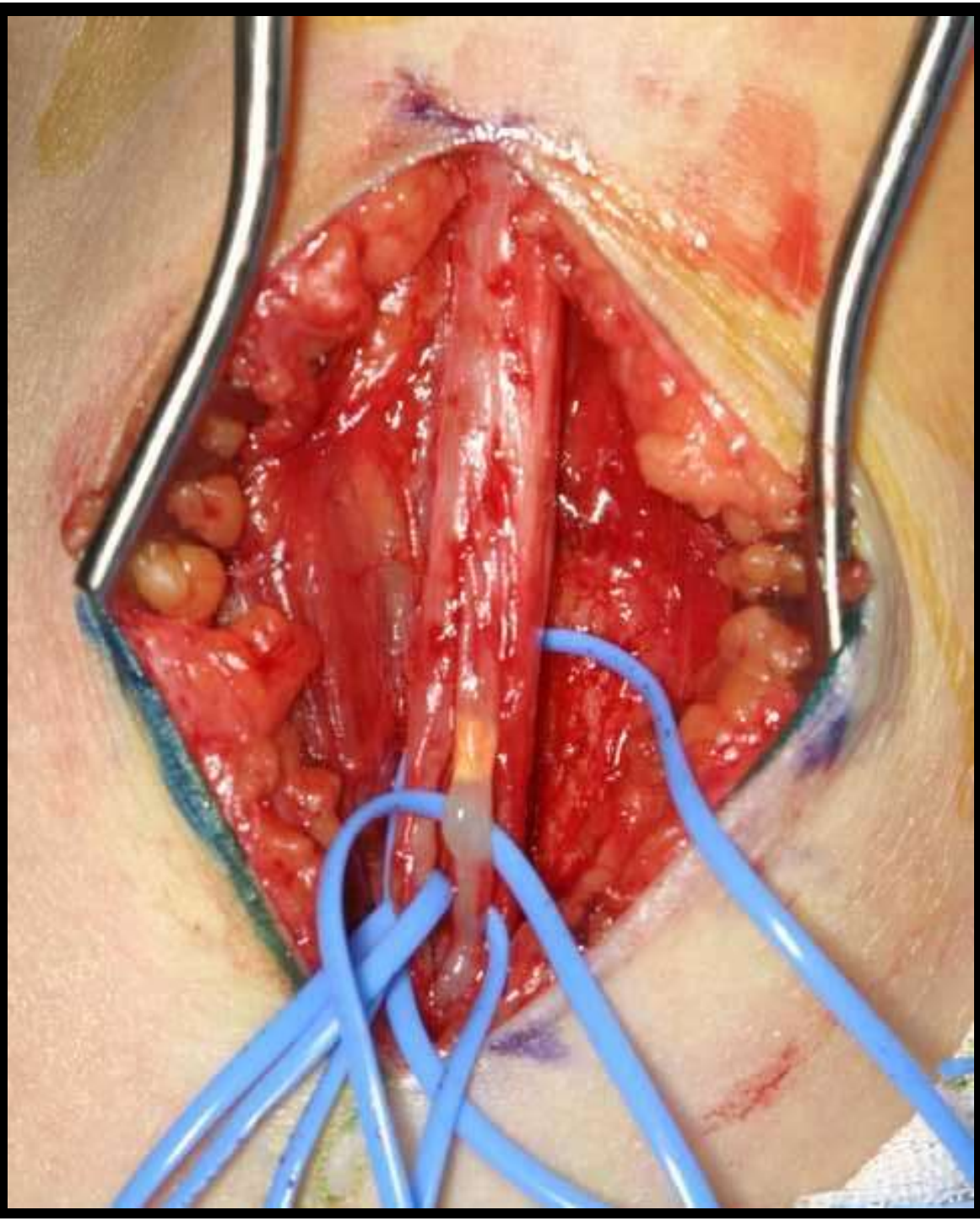

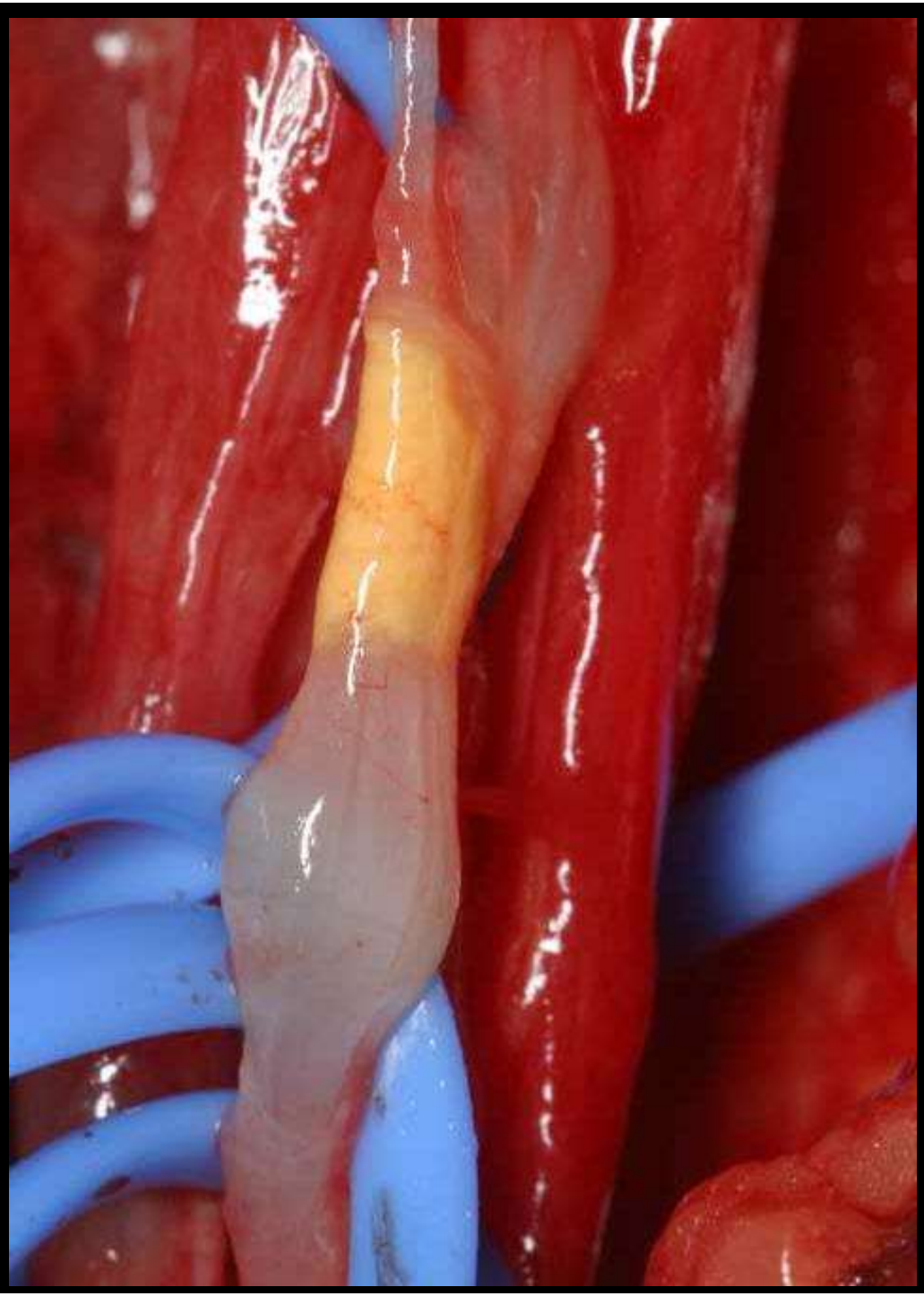


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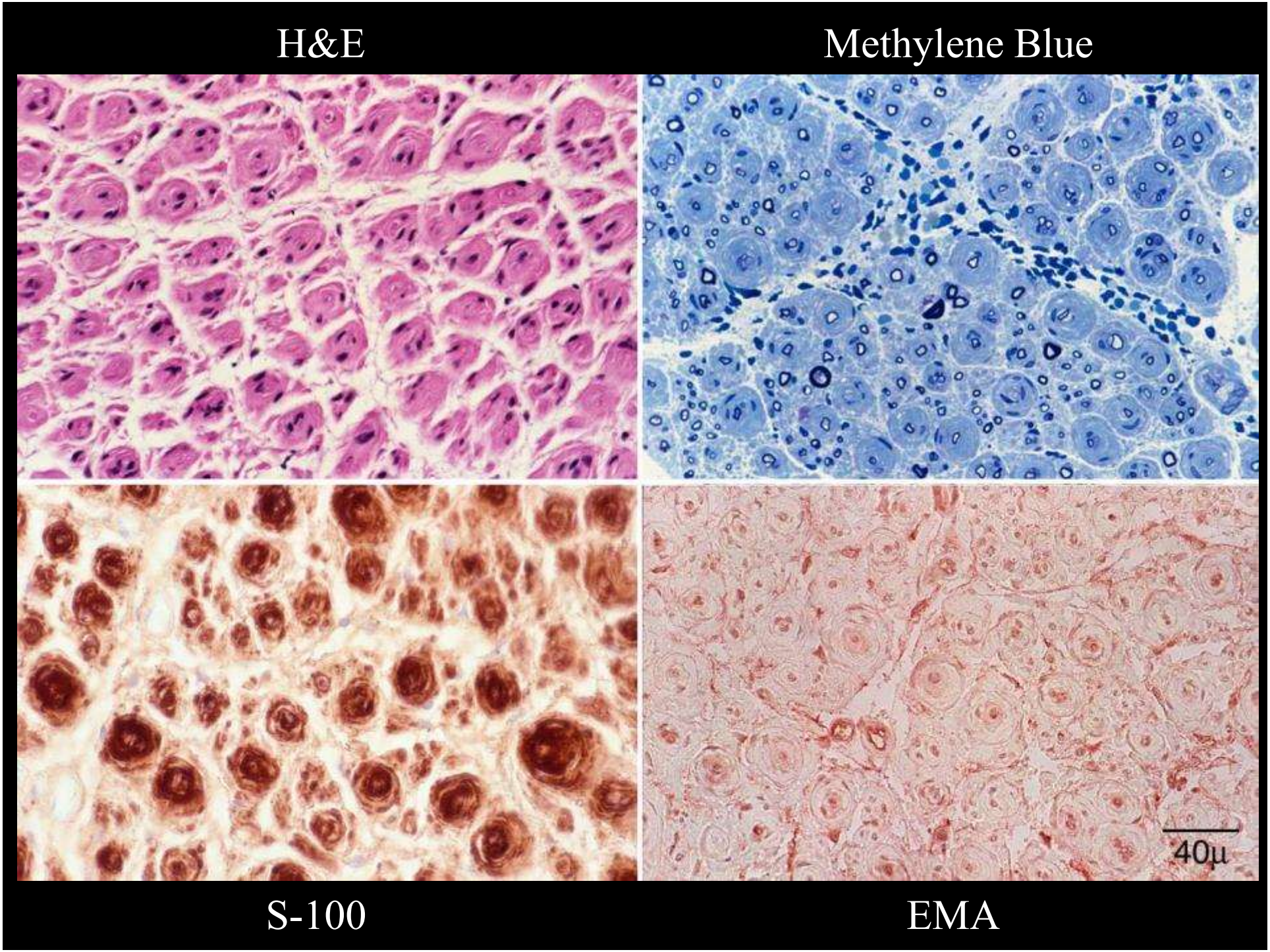
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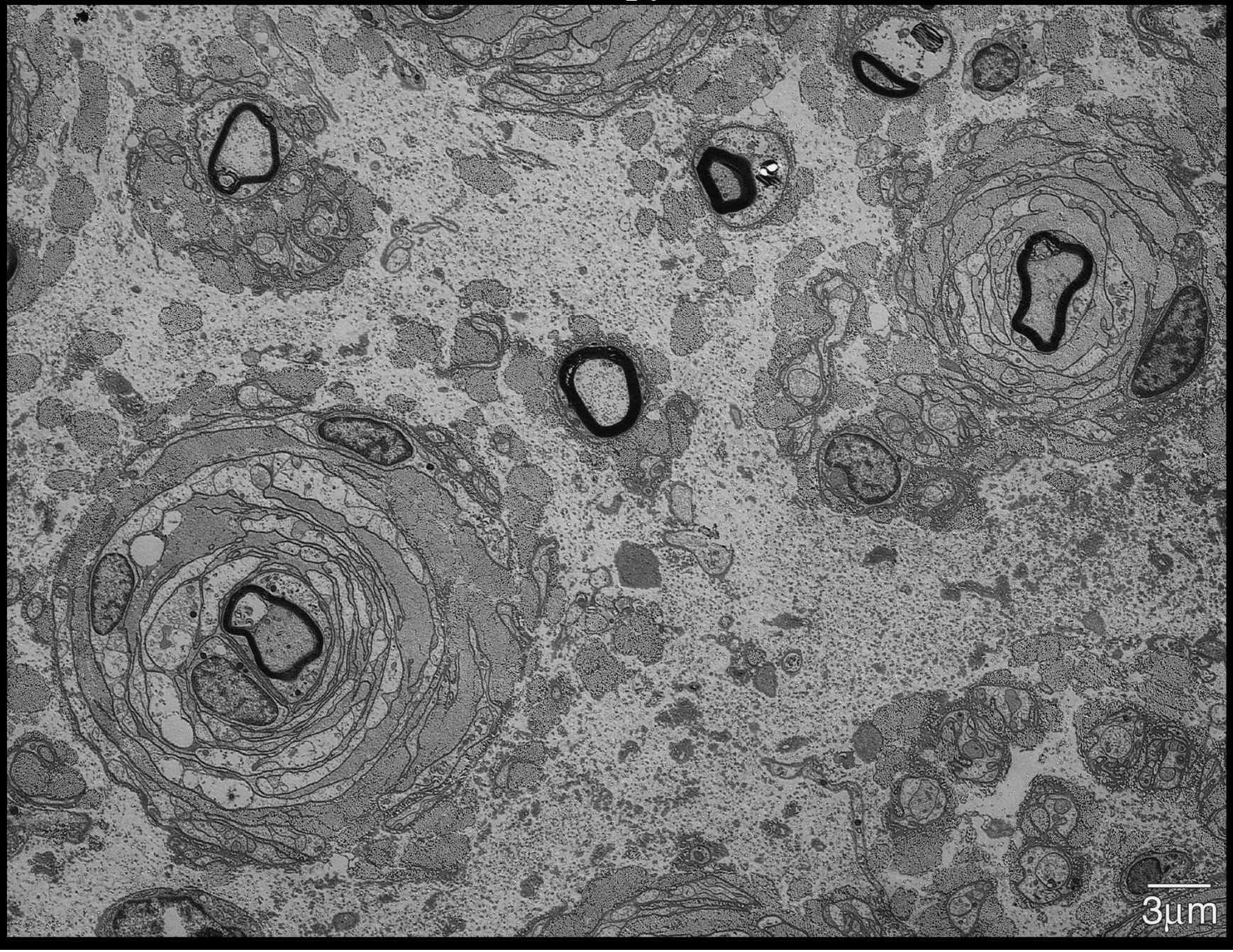
Electron Microscopy – Onion-bulbs



Case 8

- Pathology: hypertrophic neuropathy (onion-bulbs)
- Diagnosis: CIDM (focal CIDP)

Case 9

- 47 year old woman caught her left foot leaping over a fence, injured left knee and landed on left hip.
- Within days, she developed weakness and atrophy of the left leg that gradually worsened over 10 years with a foot drop.
- Neurological examination and EMG were in keeping with a left lumbosacral plexopathy (worse in peroneal nerve).
- MRI showed increase T2 signal of left lumbosacral nerve roots, plexus and sciatic nerves with some enhancement.
- A fascicular sciatic biopsy was performed.

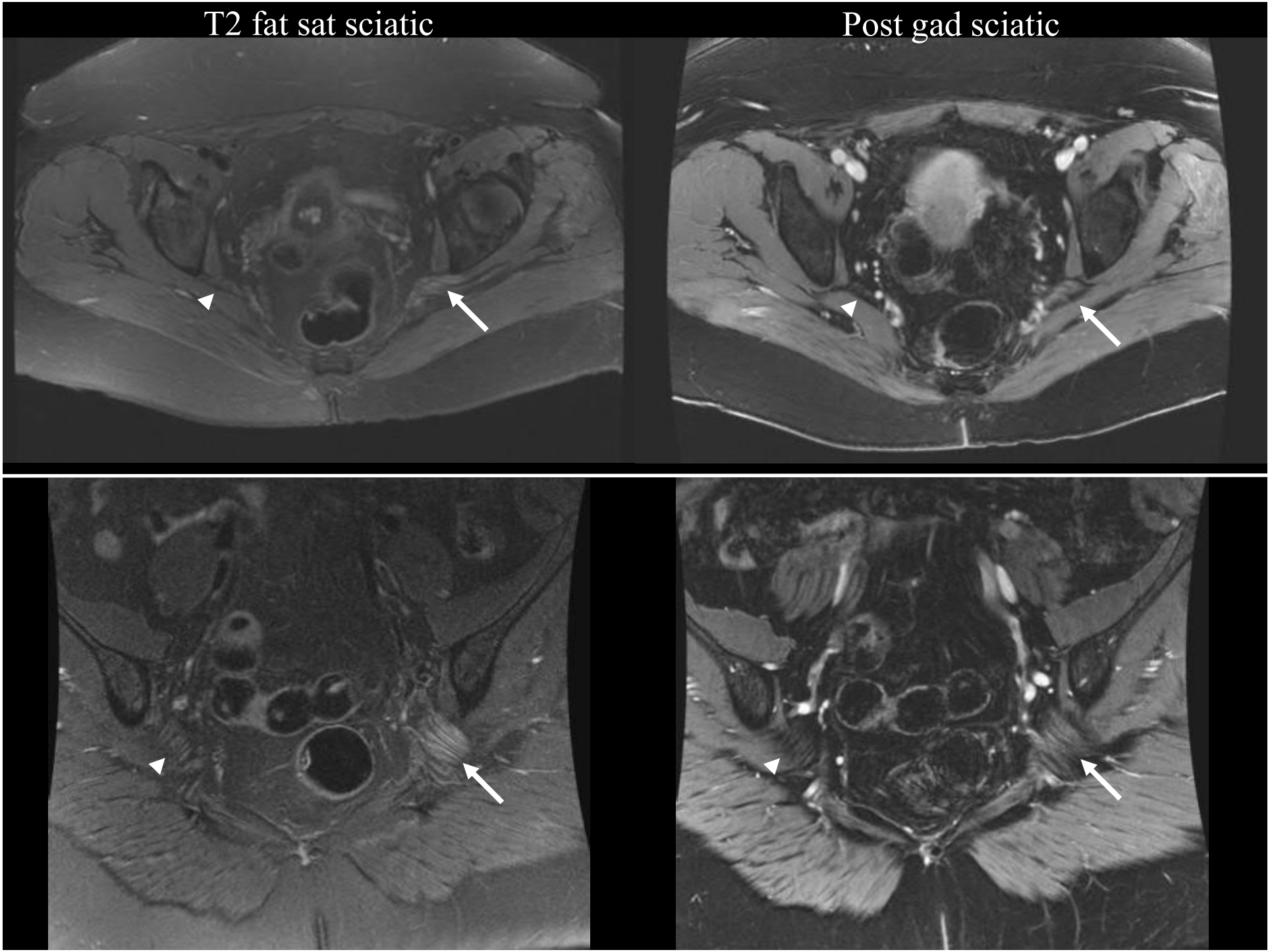
Nerve Conduction Studies

Stimulate (Record)	A (mV/μV)	CV (m/s)	DL (ms)	F (ms)
L. Peroneal motor (TA)	0.3	58	6.6	
L. Peroneal motor (EDB)	0 (>2.0)		NR (<6.6)	
L. Tibial motor (AH)	0.2 (>4.0)	35 (>40)	7.9 (<6.1)	
L. Peroneal sensory (Ankle)	0 (>0.0)		NR (<4.1)	
L. Sural sensory (Ankle)	0 (>6.0)		NR (<4.5)	
R. Peroneal motor (EDB)	6.2 (>2.0)	52 (>41)	4.9 (<6.6)	48.6
R. Tibial motor (AH)	7.2 (>4.0)	42 (>40)	4.1 (<6.1)	59.6
R. Sural sensory (Ankle)	14 (>6.0)		3.4 (<4.5)	

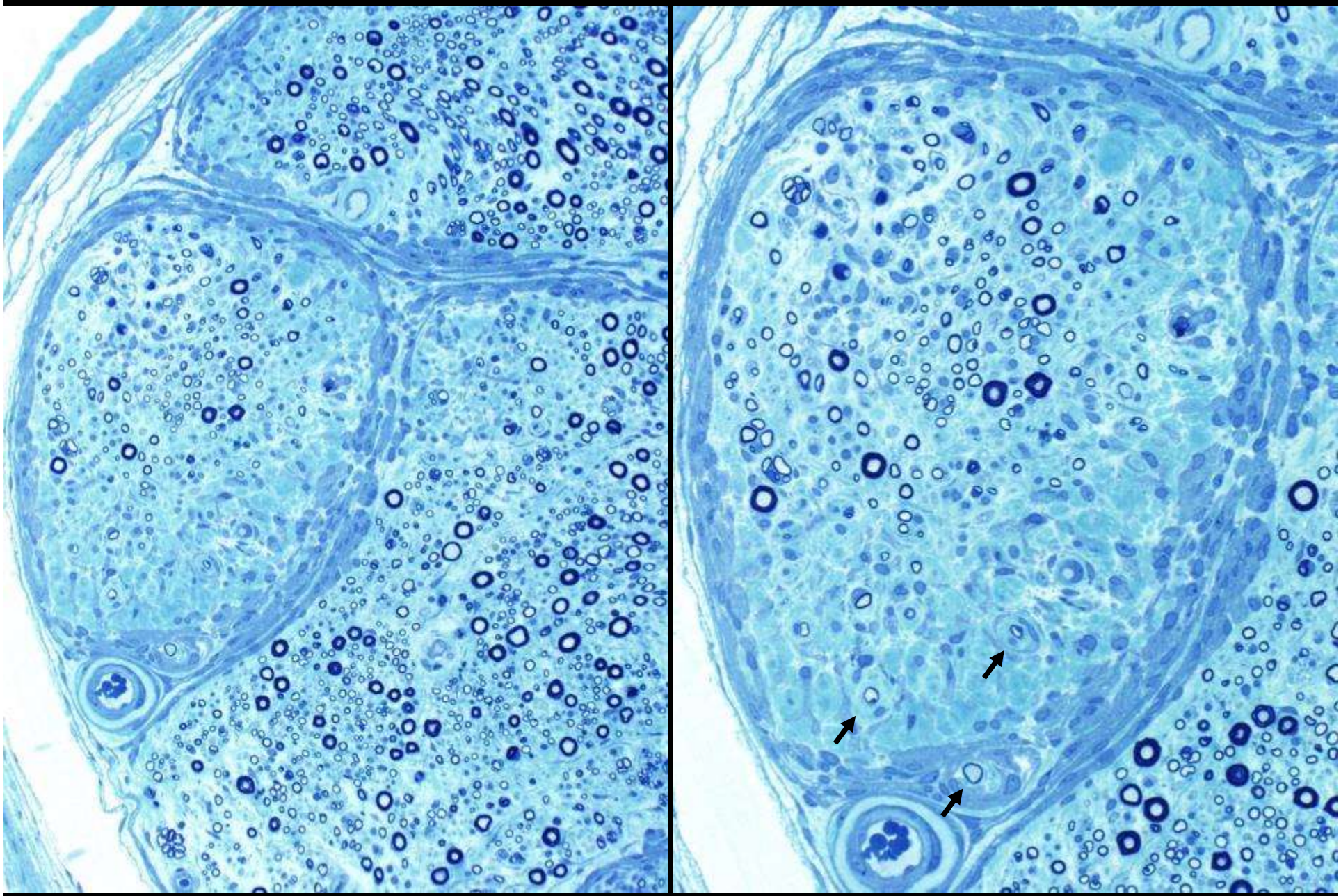
EMG

Muscle	Insertional activity	Fibrillation	Fasciculation	MUP
L. Tibialis Anterior	Increased	++	0	
L. Medial Gastroc	Increased	++	0	1+ big
L. Tensor fasciae latae	Increased	+	0	1+ big
L. Vastus medialis	Normal	0	0	Normal
L. Biceps femoris (short head)	Increased	+	0	1+ big
L. Biceps femoris (long head)	Increased	+	0	1+ big
L. Gluteus maximus	Increased	++	0	1+ big
L. Lumbar parapspinals	Normal	0	0	Normal
L. S1 Paraspinal	Normal	0	0	Normal
R. Tibialis Anterior	Normal	0	0	Normal
L. First dorsal interosseous	Normal	0	0	Normal

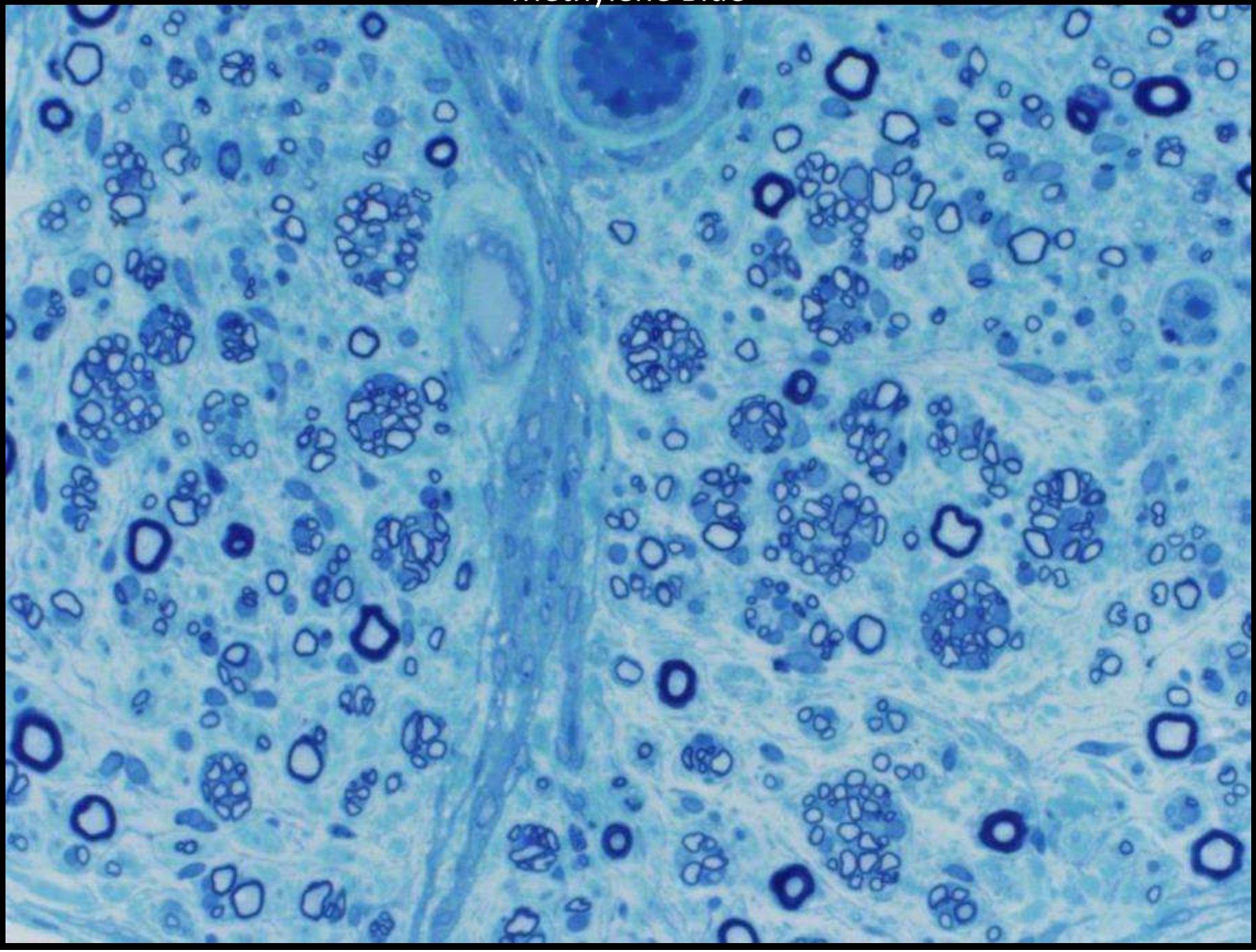
- Interpretation: Active left lumbosacral plexopathy


T2 fat sat sciatic
Post gad sciatic

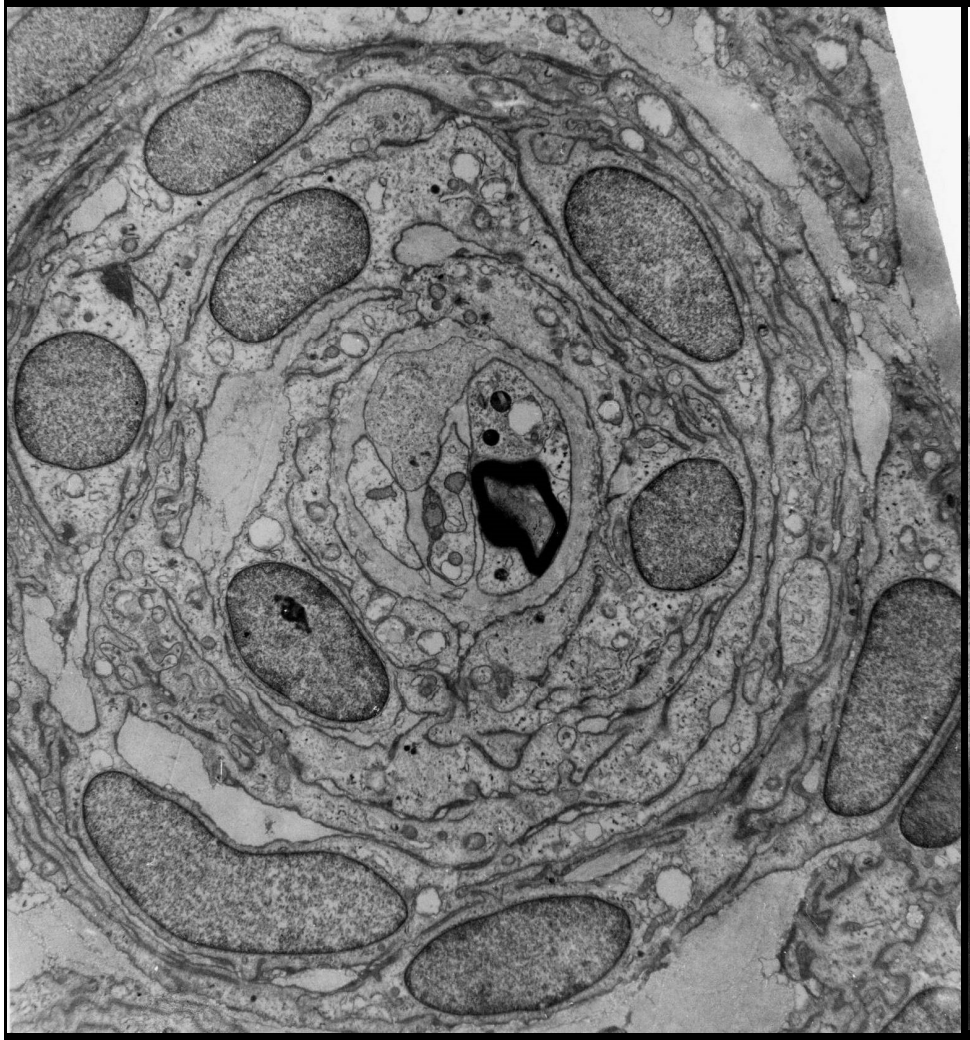
Methylene Blue

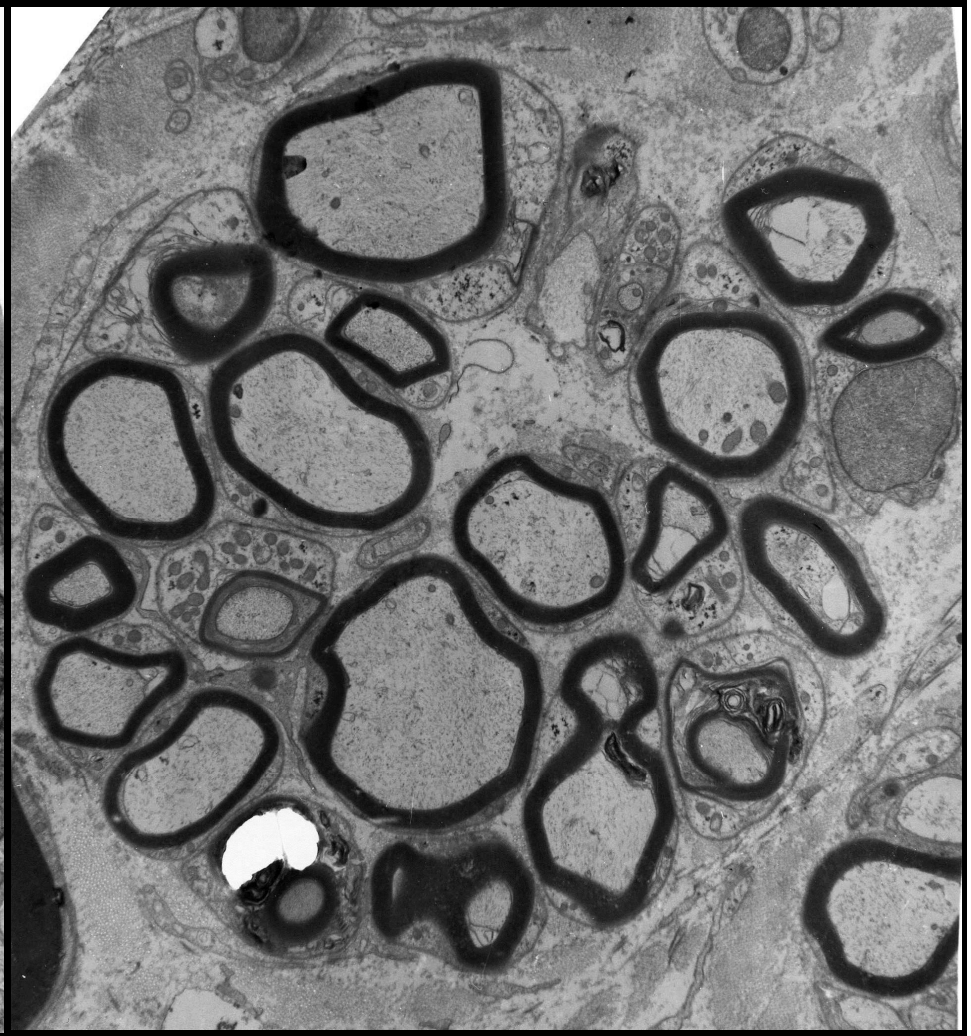


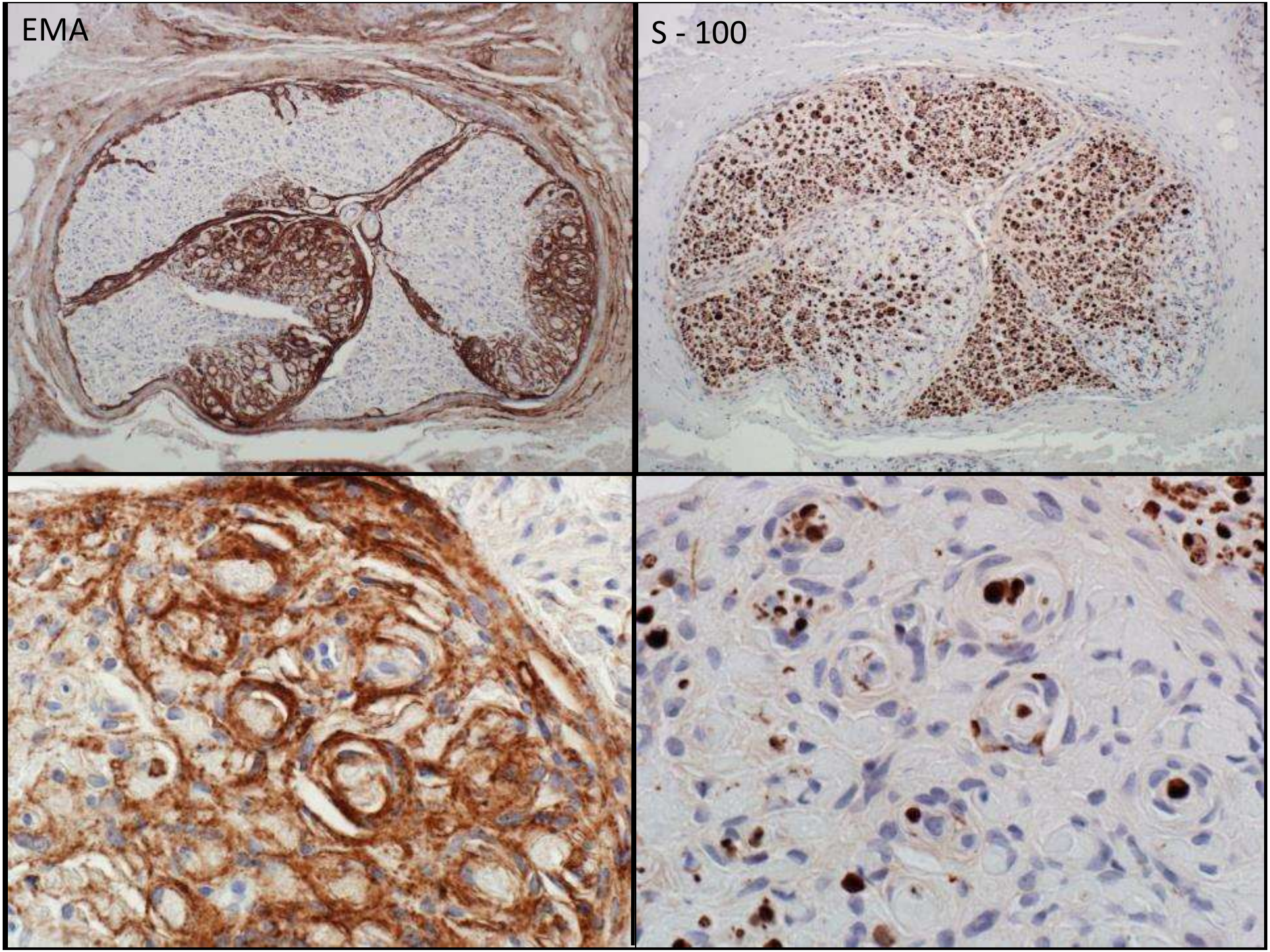
Methylene Blue



EM





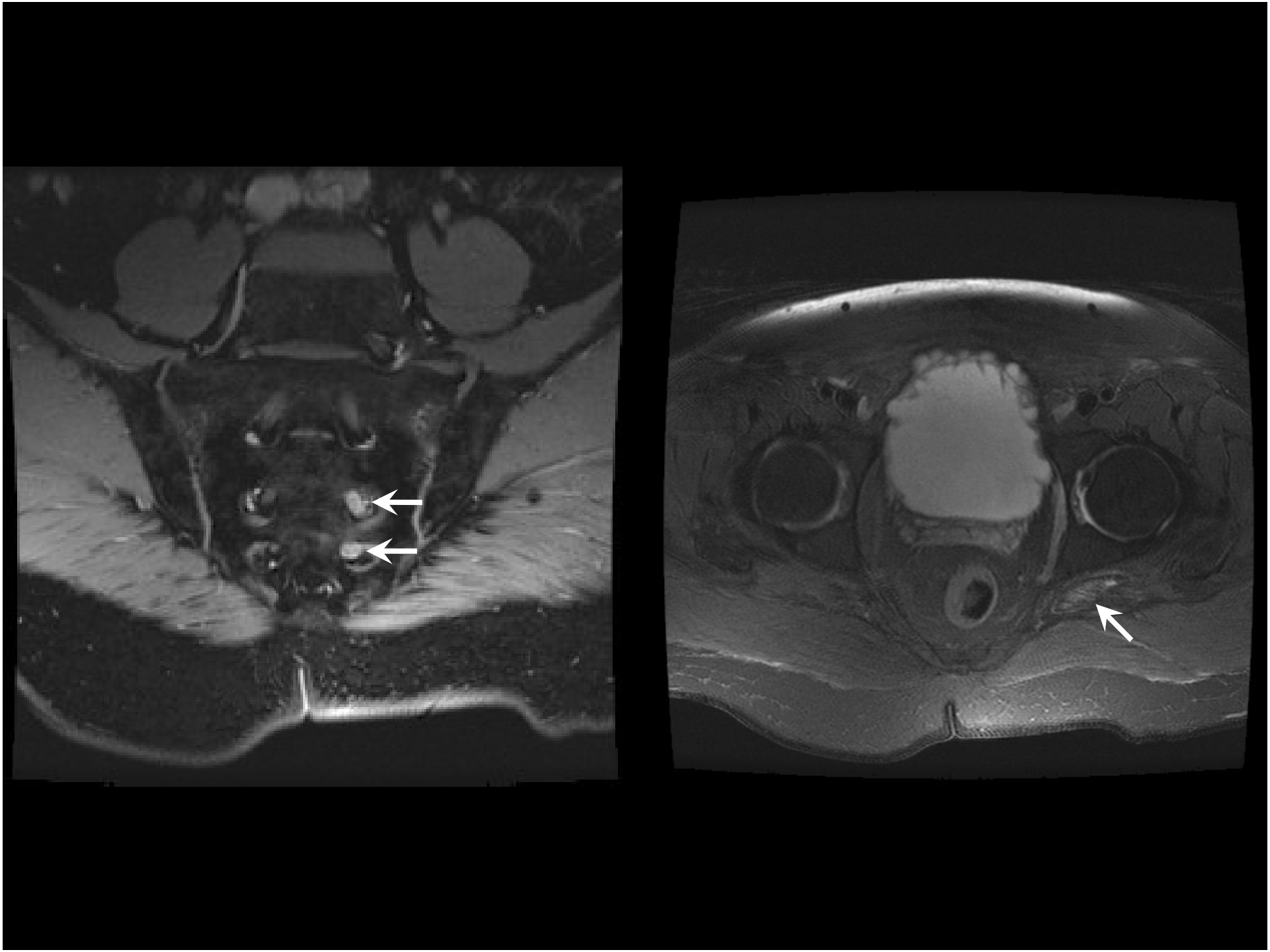

EMA
S - 100

Case 9

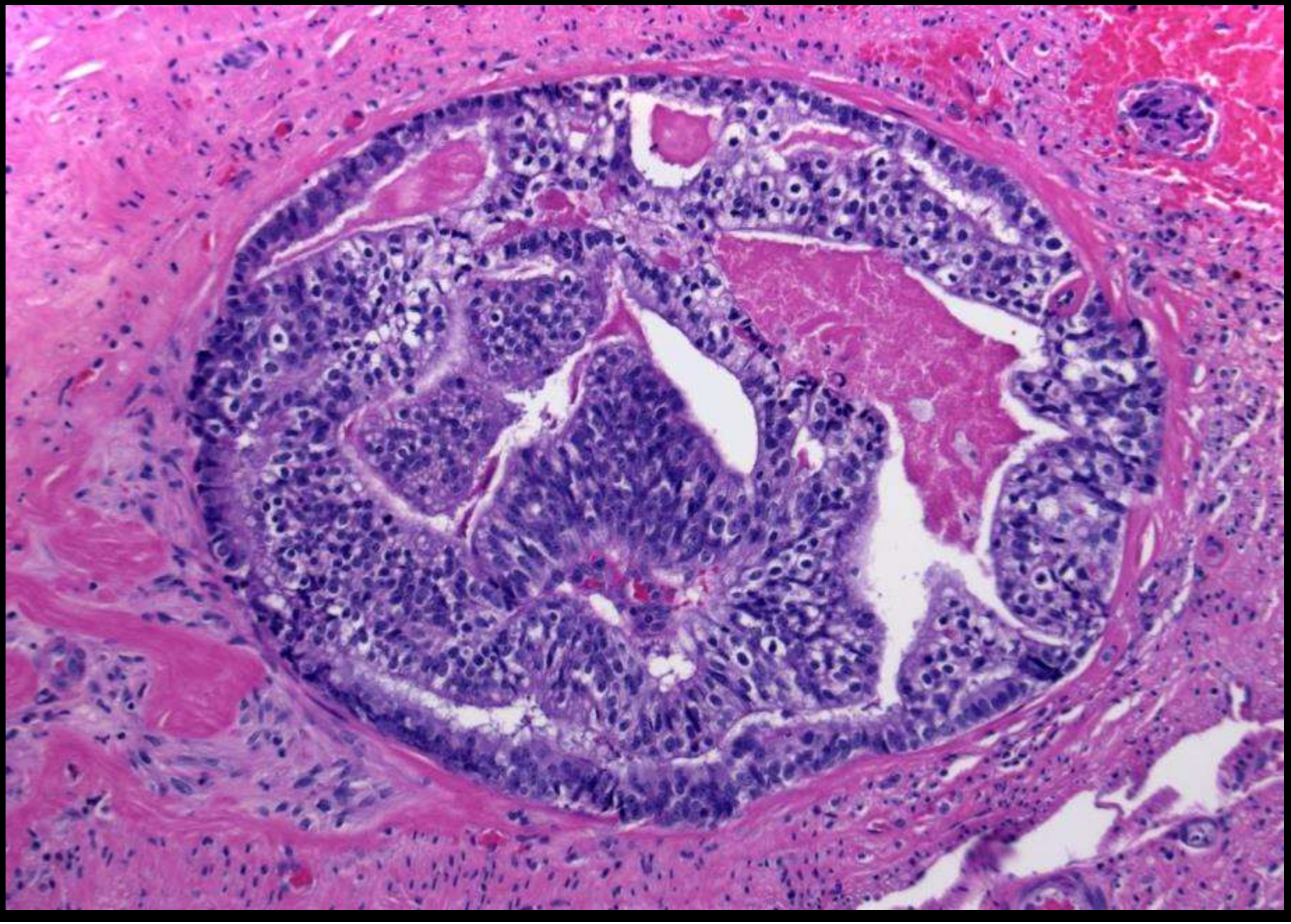
- Pathology
  - fields of regenerating clusters
  - areas at the edge of the fascicles with microfasciculation and injury neuroma
- Diagnosis: intraneural traumatic injury neuroma
- Treatment: none

Case 10

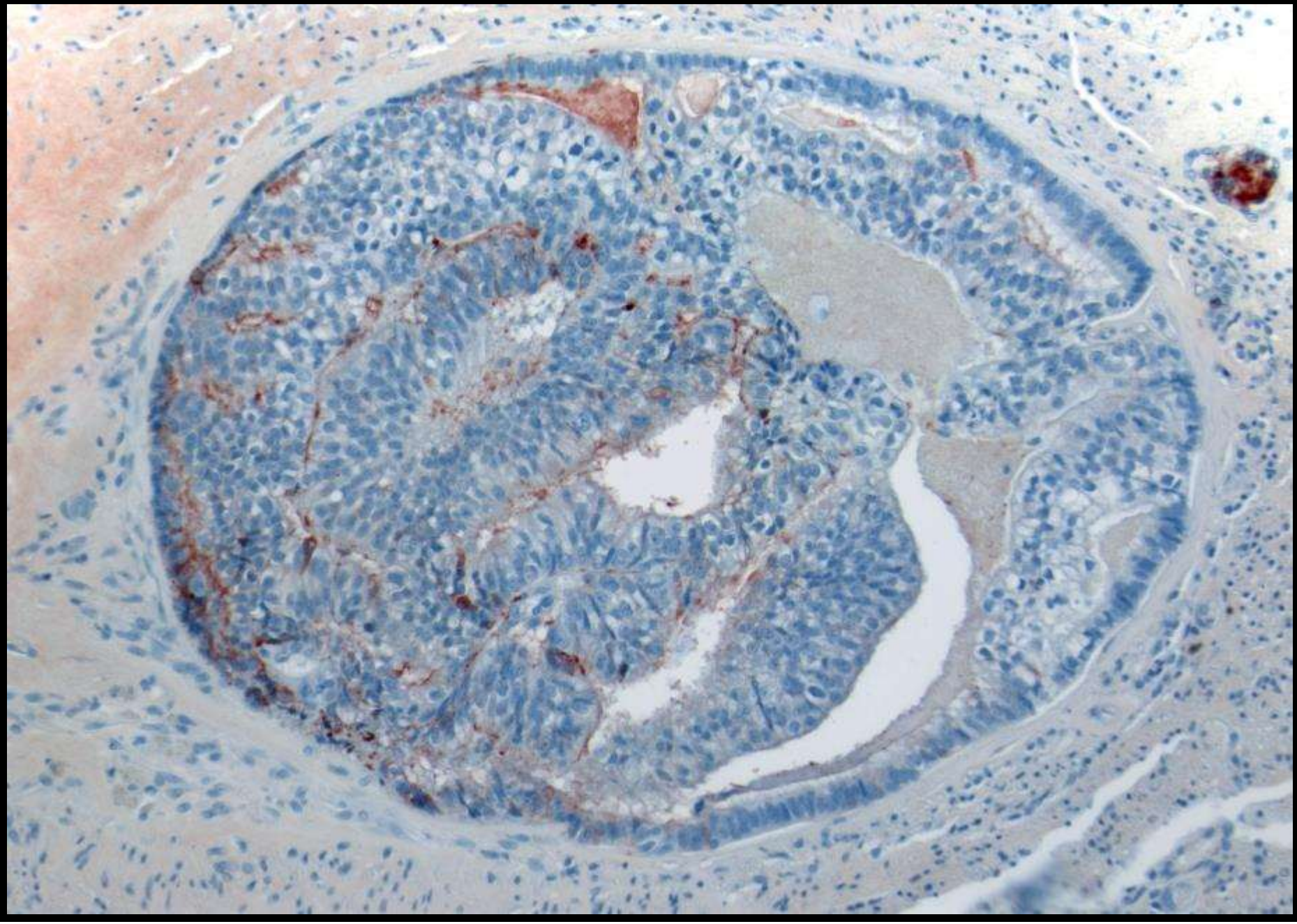
- 60 year old diabetic man with 3 years of left leg pain, numbness and weakness, bladder incontinence and erectile dysfunction.
- Weak hamstrings and gluteal muscles. Decreased perianal sensation.
- EMG showed denervation and large MUPs in sacral innervated muscles.
- MRI showed enlargement and enhancement of the S2 and S3 roots into the sciatic nerve.
- An S2 rootlet biopsy was performed.



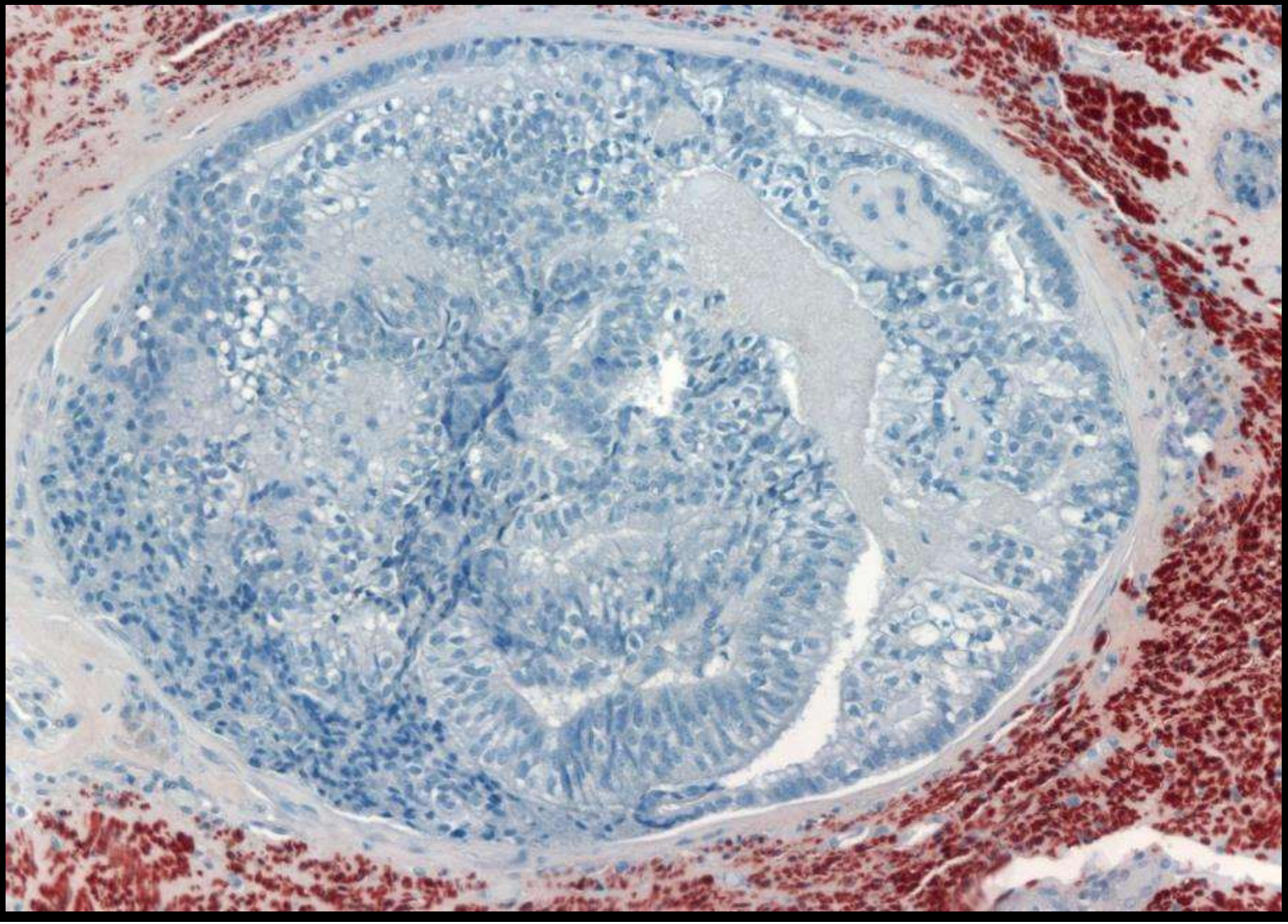
H&E



PSA



S-100

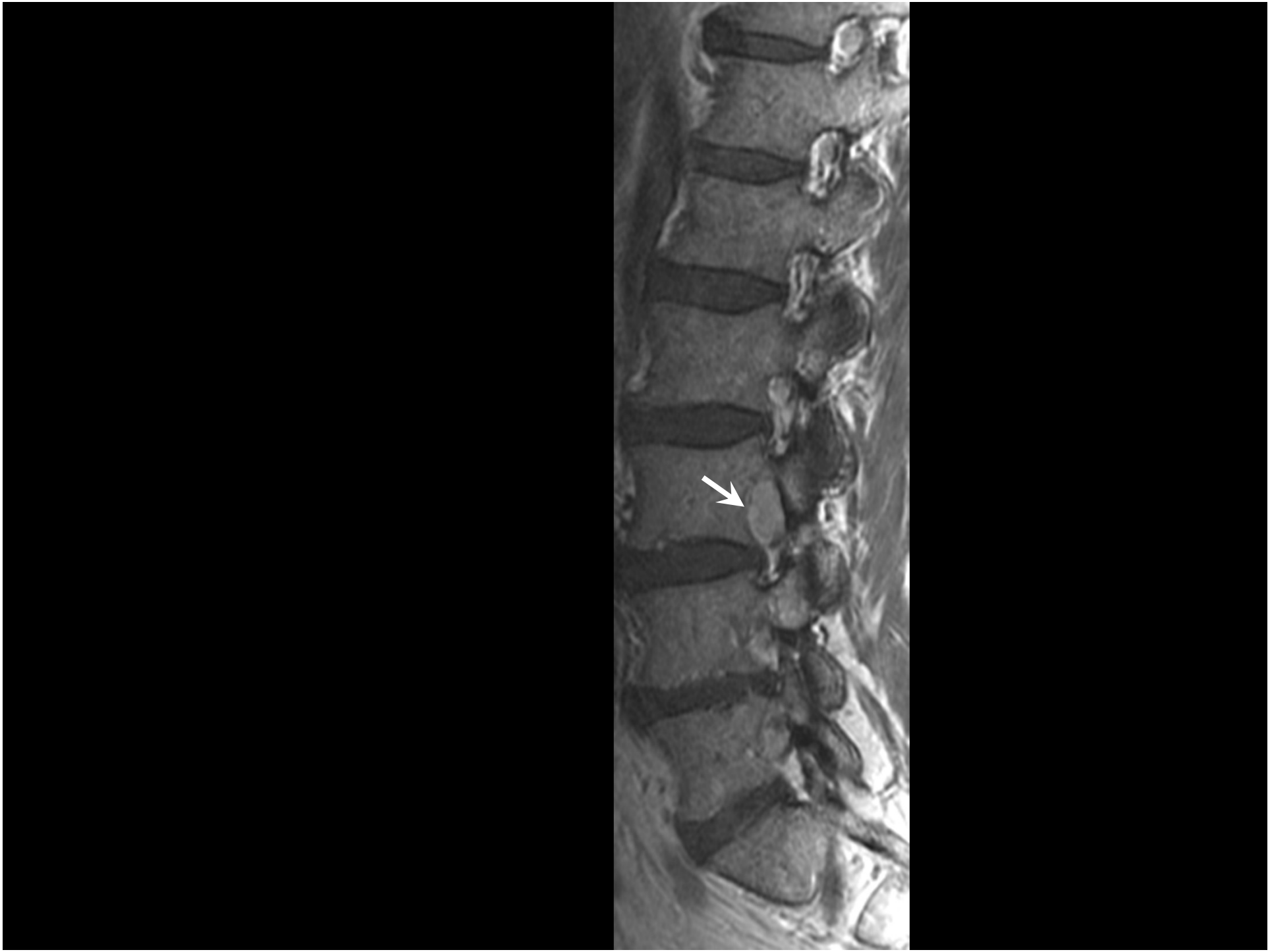


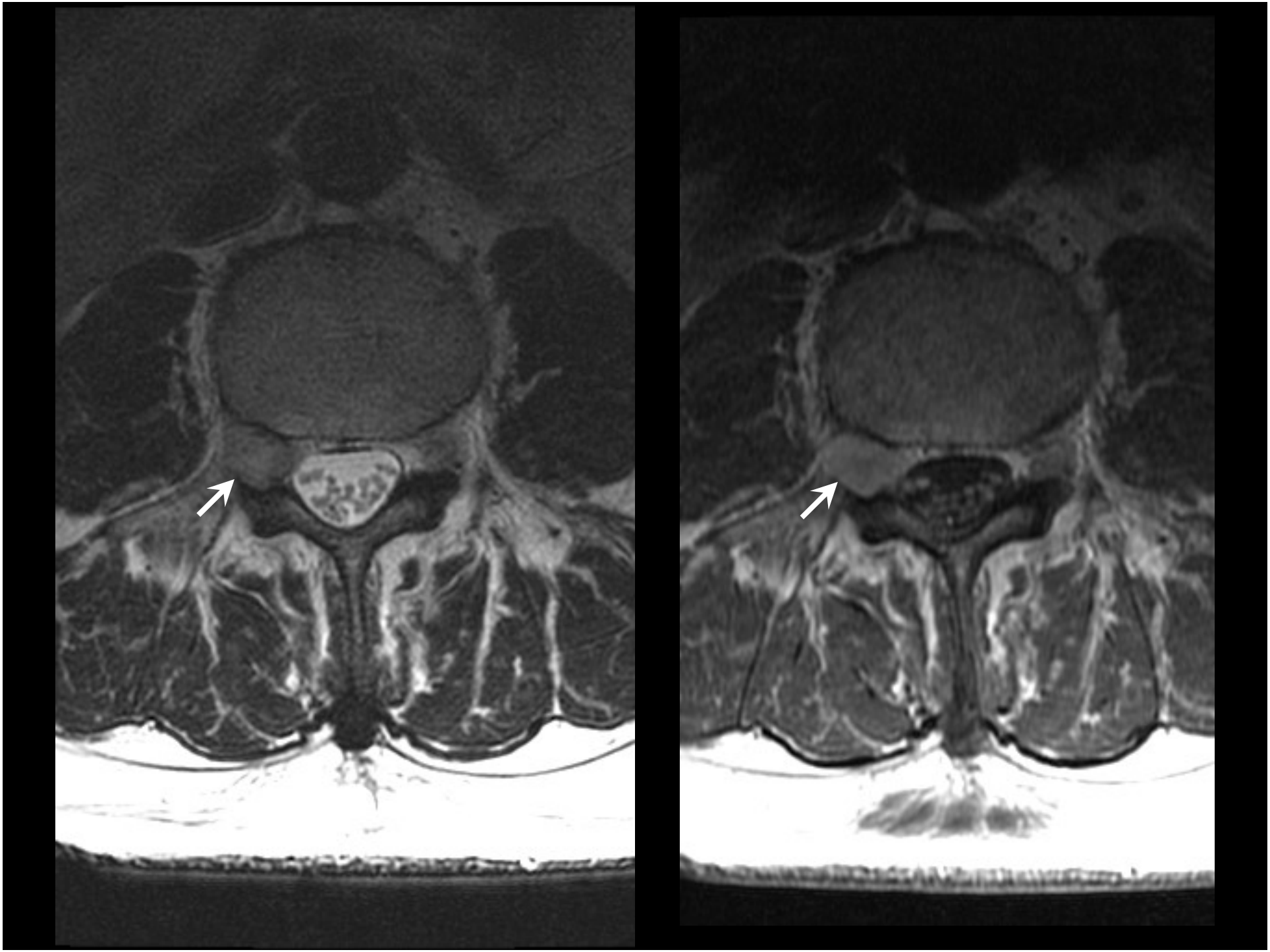
Case 10

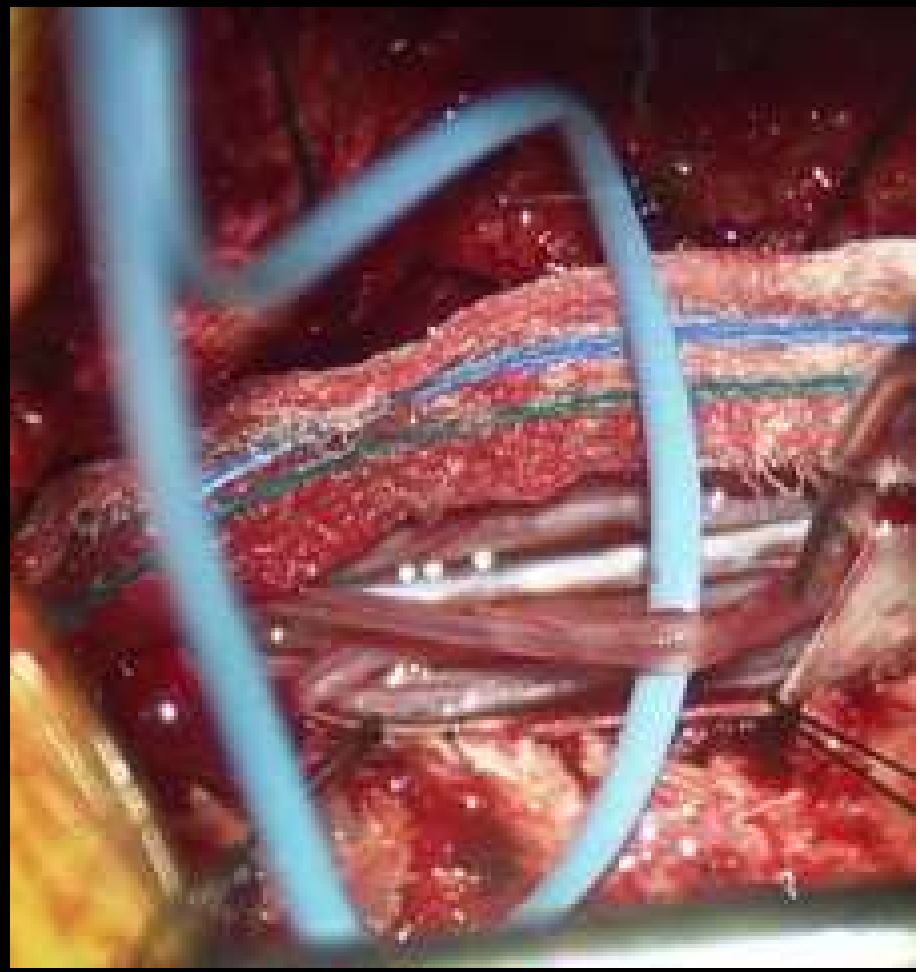
- Pathology: adenocarcinoma
- Diagnosis: metastatic prostate cancer in the sacral nerve roots by perineurial spread

Case 11

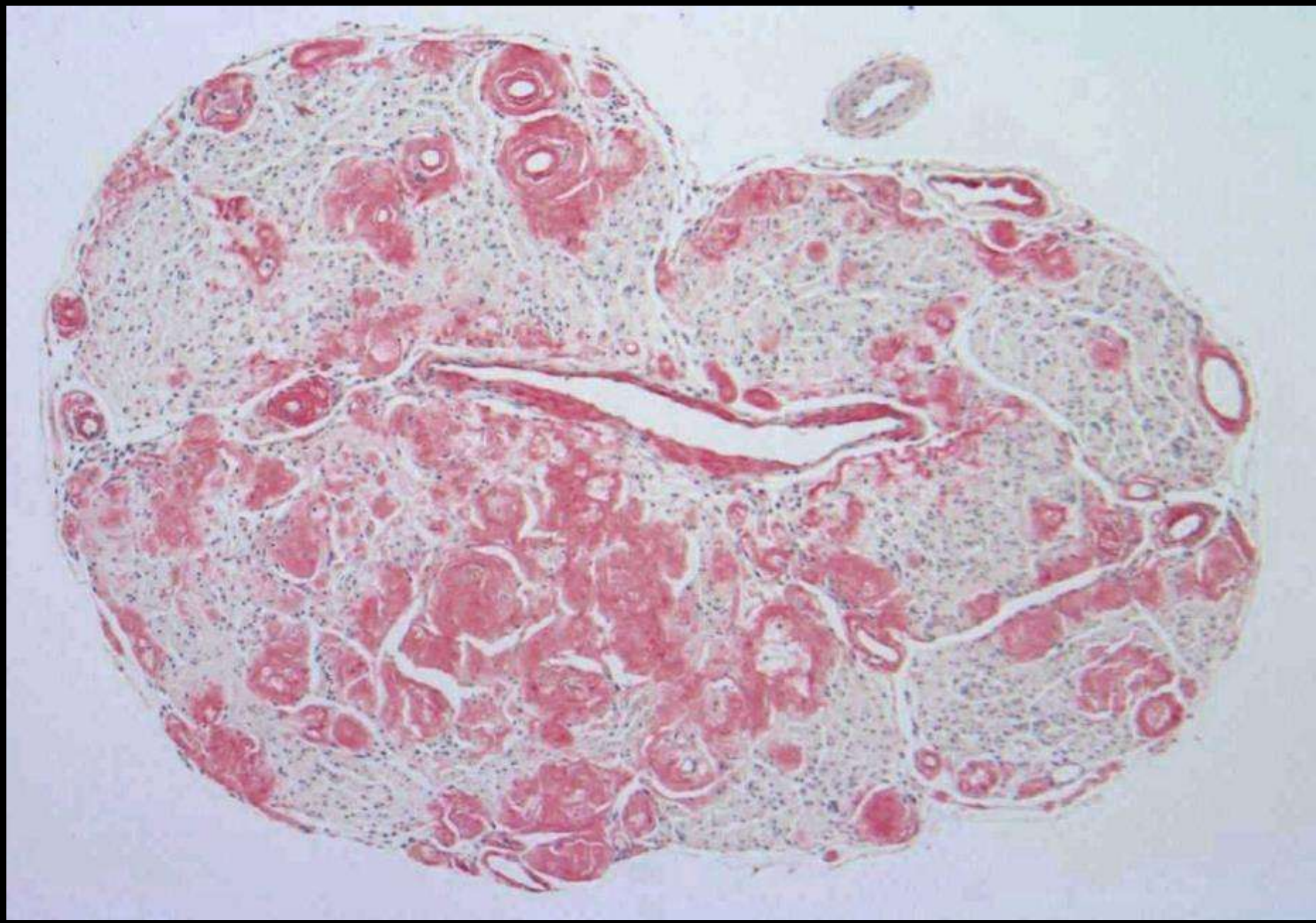
- 72 year old man with 6 years of bilateral lower limb numbness and weakness, and 3 months of bowel and bladder incontinence.
- IgM Kappa monoclonal protein.
- Neurological examination and EMG showed axonal lumbosacral polyradiculopathy.
- MRI showed a right L3-4 foraminal mass and thickening and enhancement of the cauda equina nerve roots.
- A lumbar rootlet biopsy was performed.



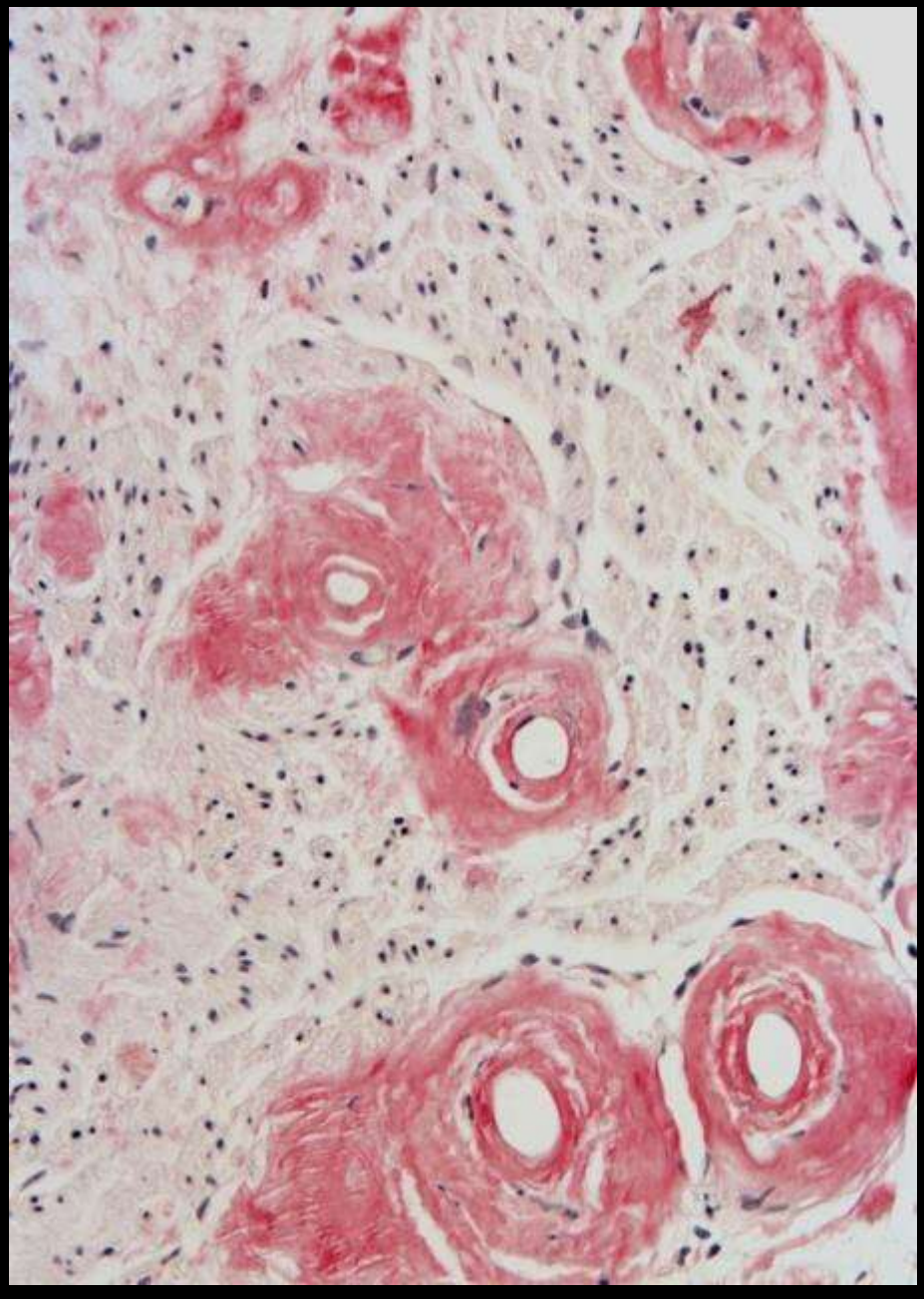




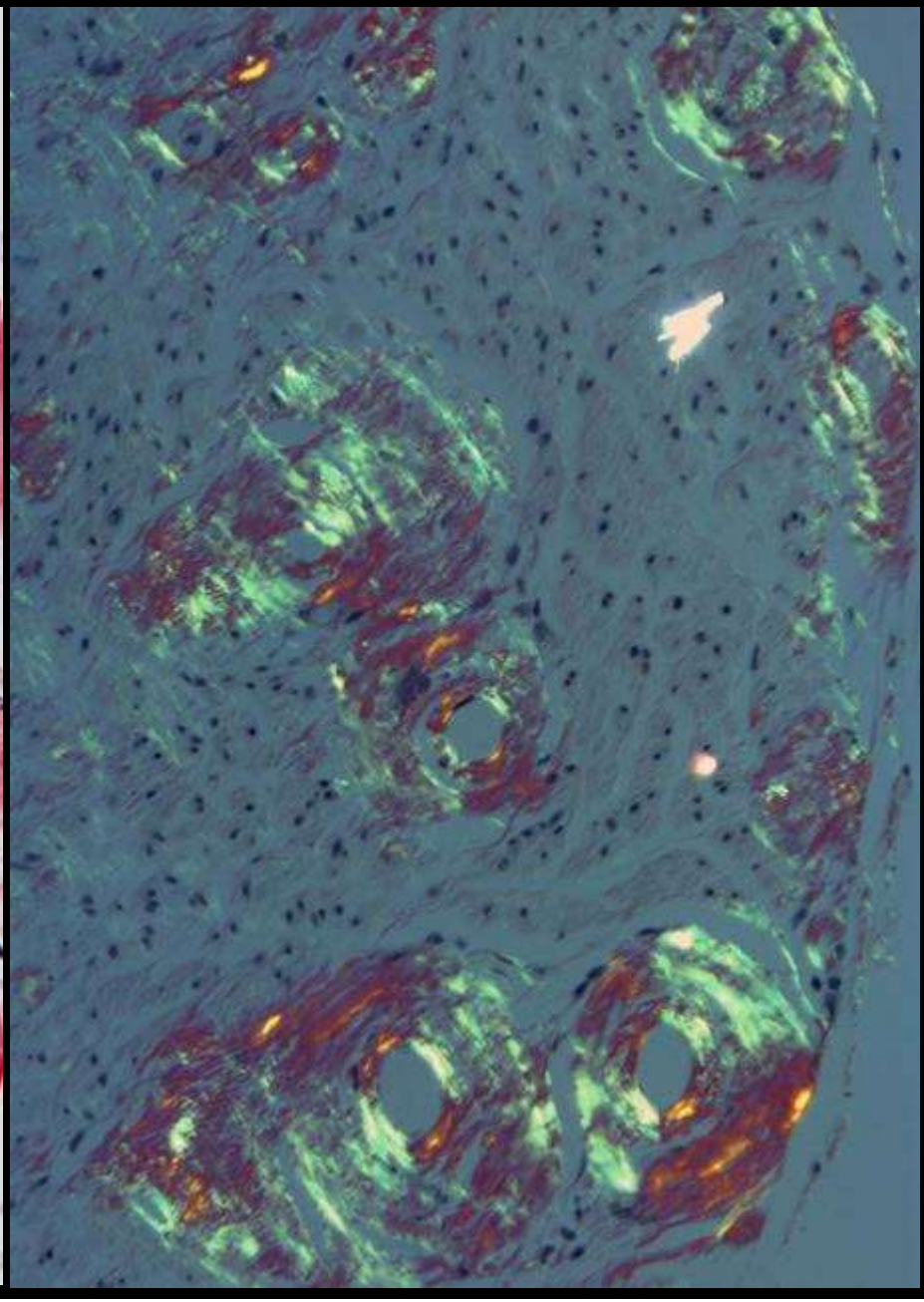
Congo Red



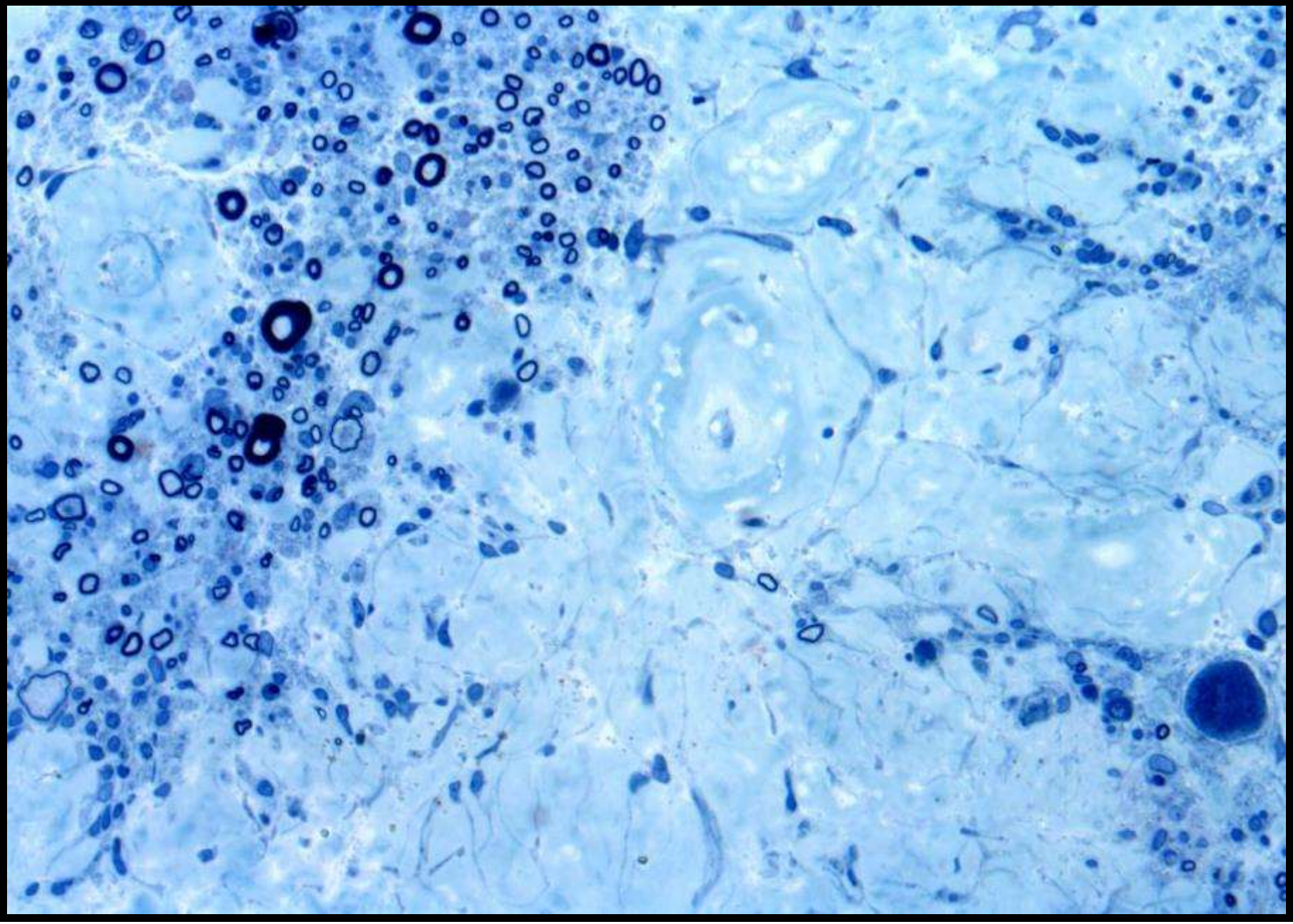
Congo Red



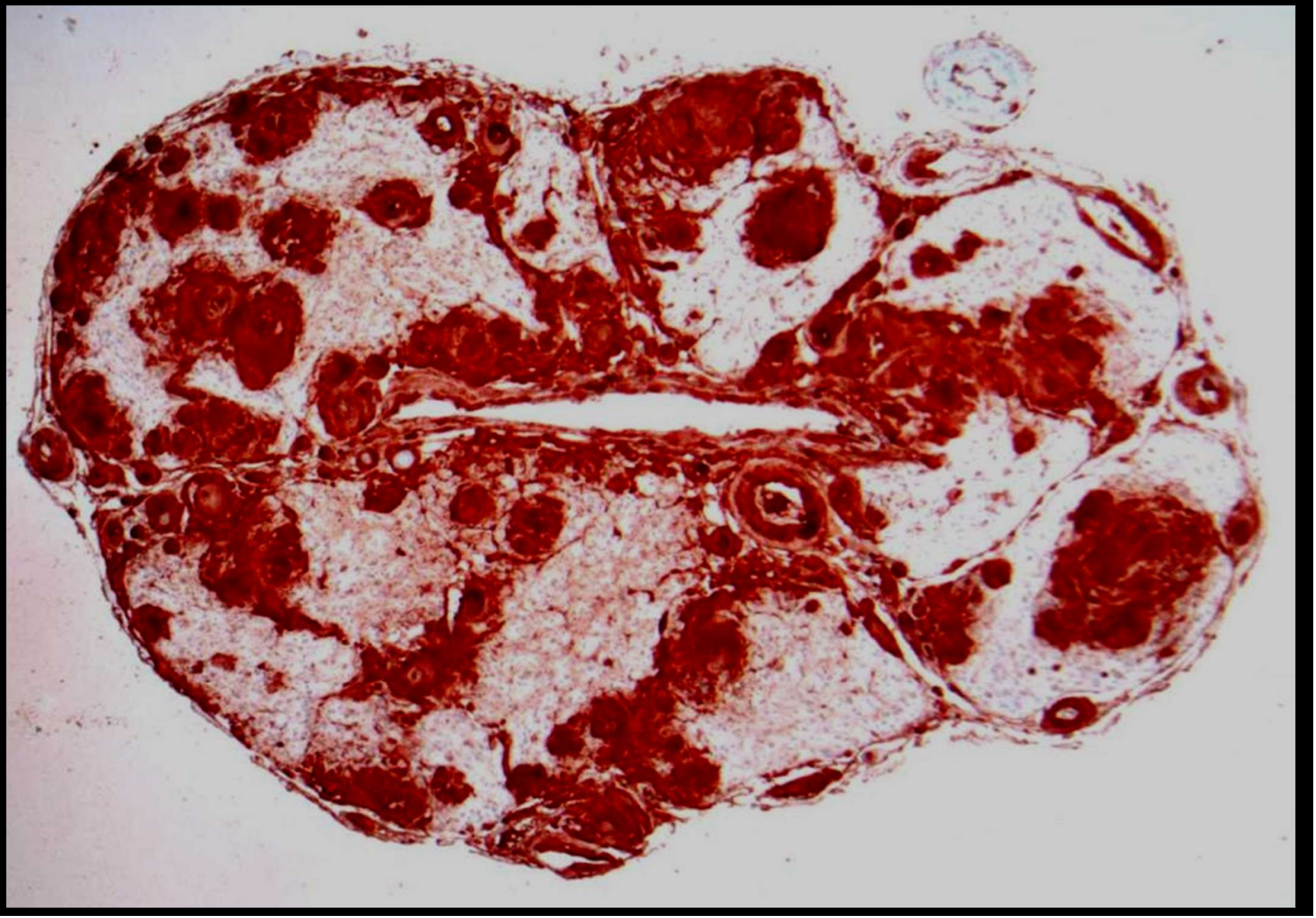
Congo Red (apple-green birefringence)



Methylene Blue



Kappa



Case 11

- Pathology: amyloidosis, positive for kappa
- Diagnosis: lumbar root amyloidoma
- Treatment: removal of L3-4 foraminal tumor

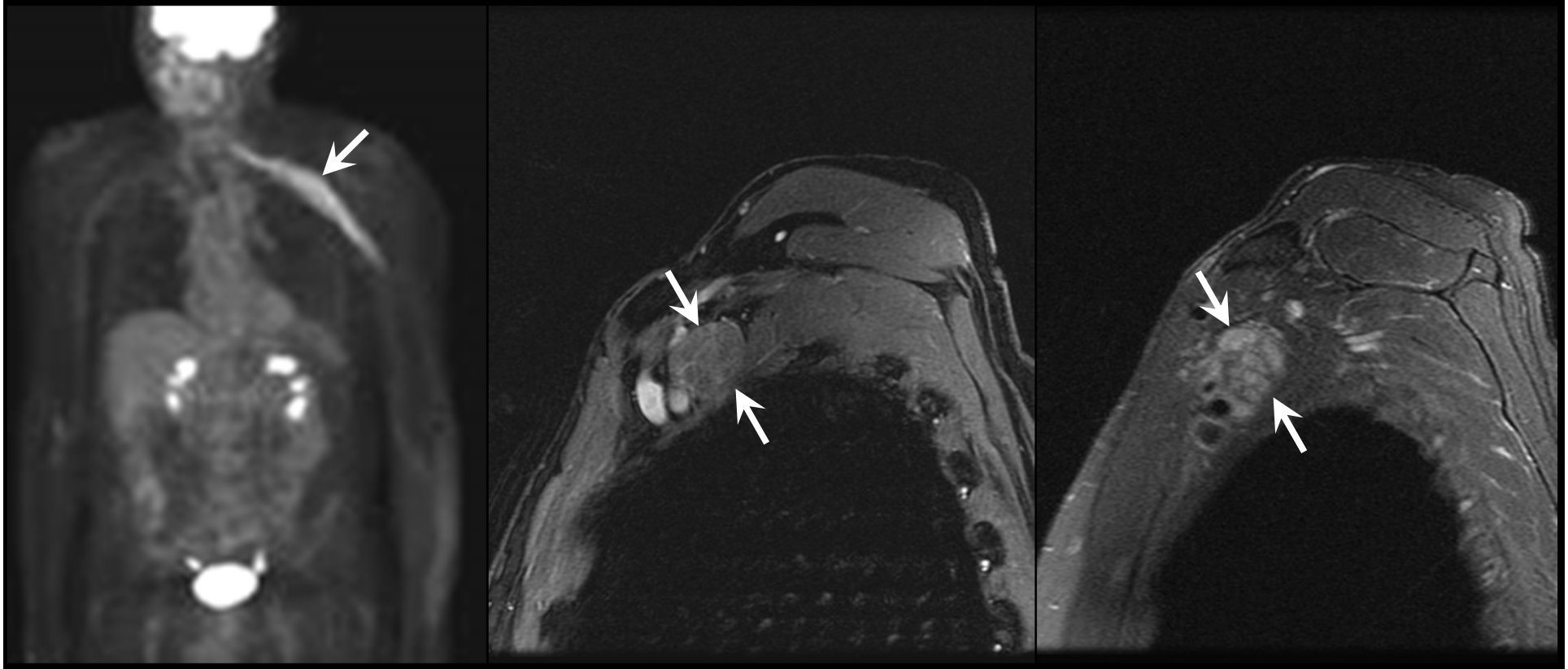
Case 12

- 70 year old man with 2 years of slowly progressive numbness of left 4th and 5th fingers and weakness of ulnar greater than median muscles.
- Ulnar nerve transposition surgery was performed without benefit.
- EMG showed a chronic severe left lower trunk brachial plexopathy and the CSF showed a protein of 48 mg/DL, 53 WBCs and myeloblasts on cytology.
- MRI demonstrated marked fusiform enlargement of entire brachial plexus with enhancement and PET scan showed avid uptake on the brachial plexus.
- A brachial plexus biopsy was performed.

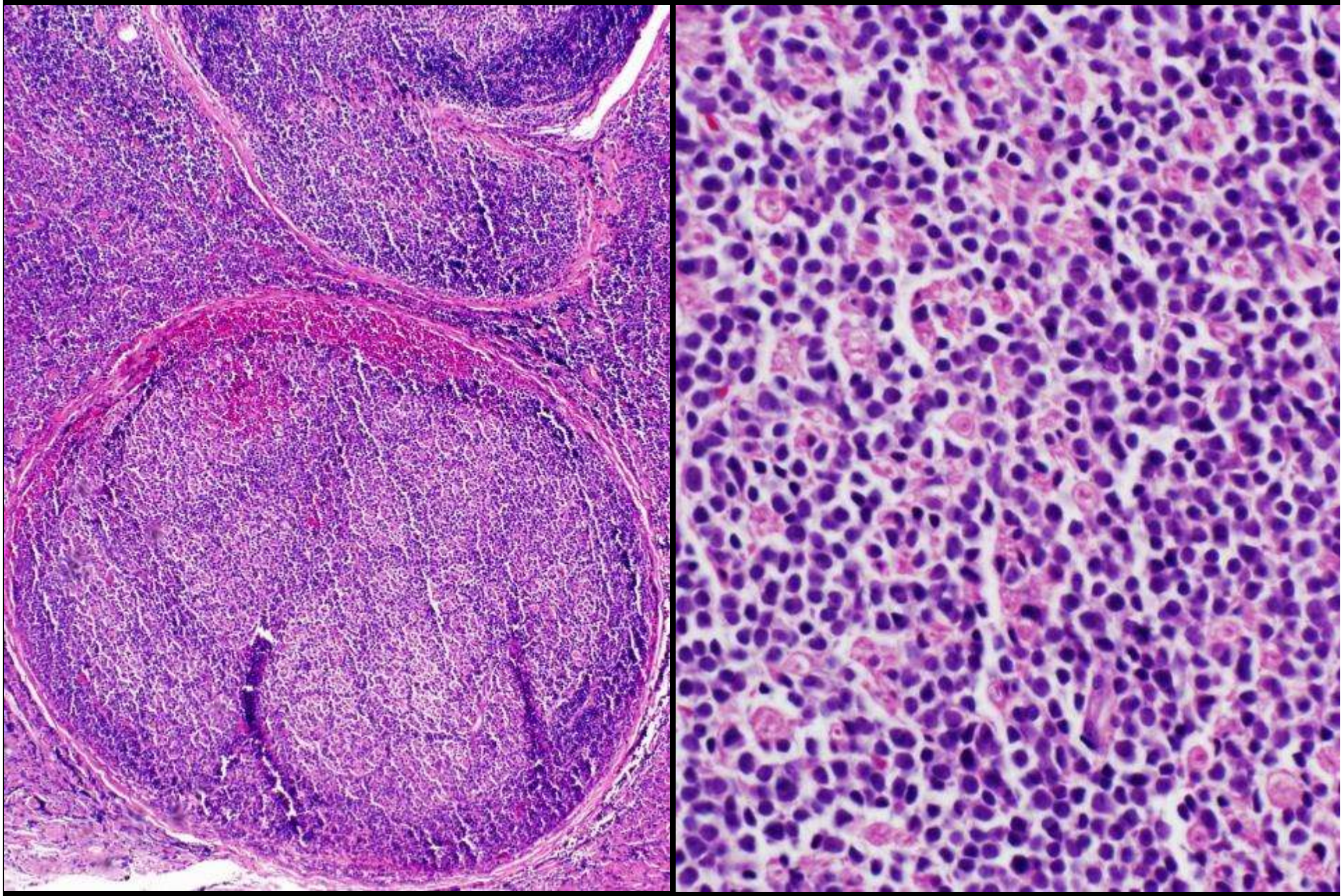
PET

MRI
Post-gad T_1 with fat sat

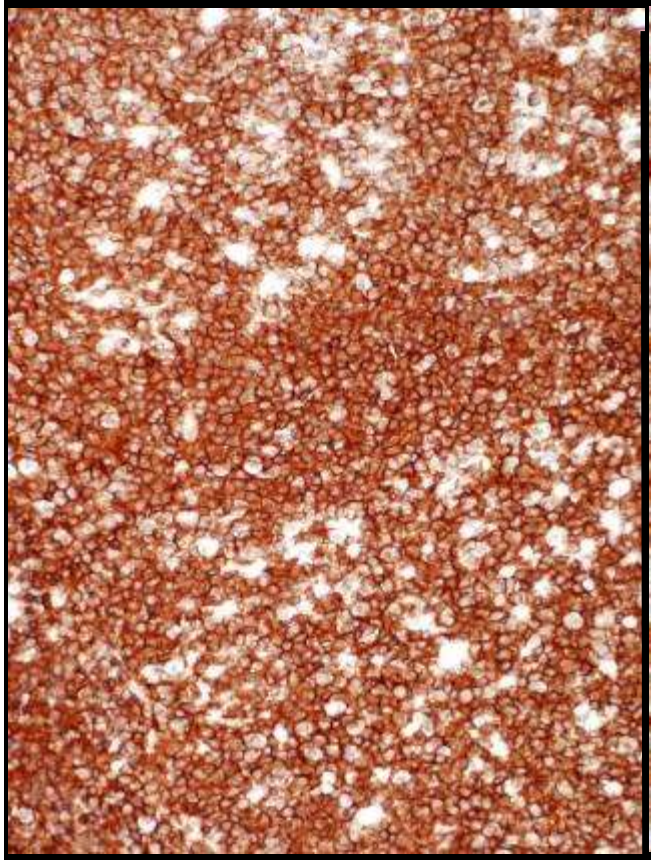
MRI
FSE T_2 with fat sat



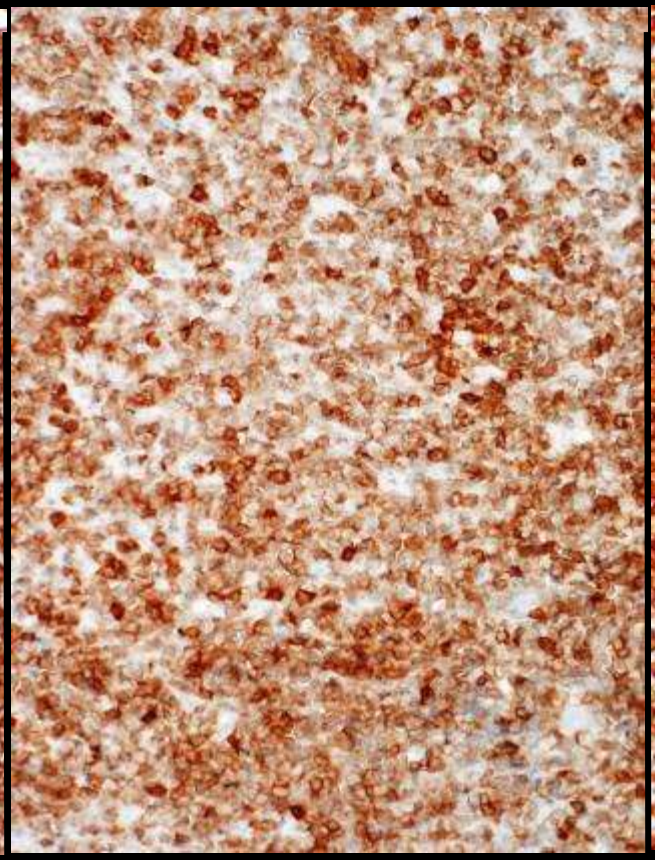
H&E



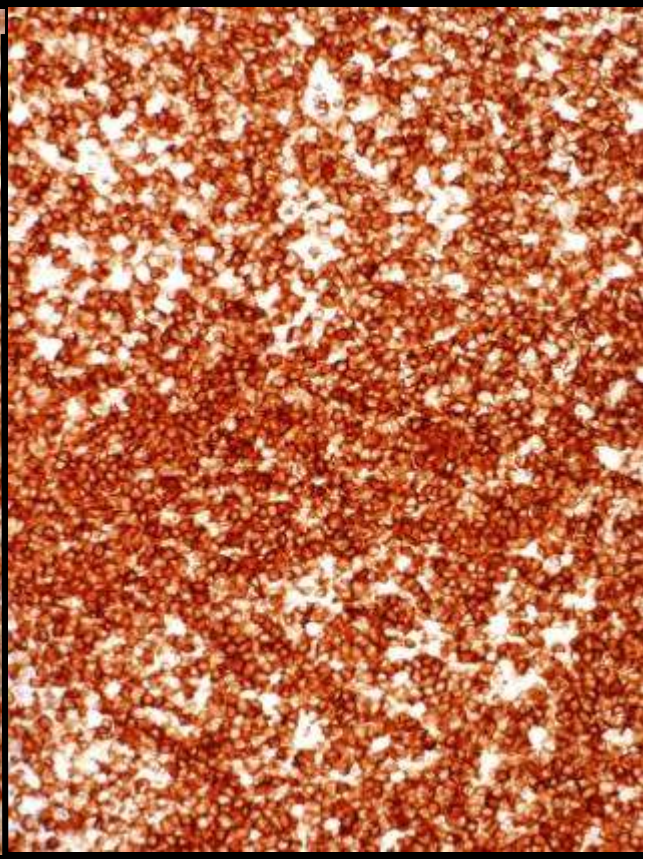
CD45 (lymphocytes)



CD33 (myeloid)

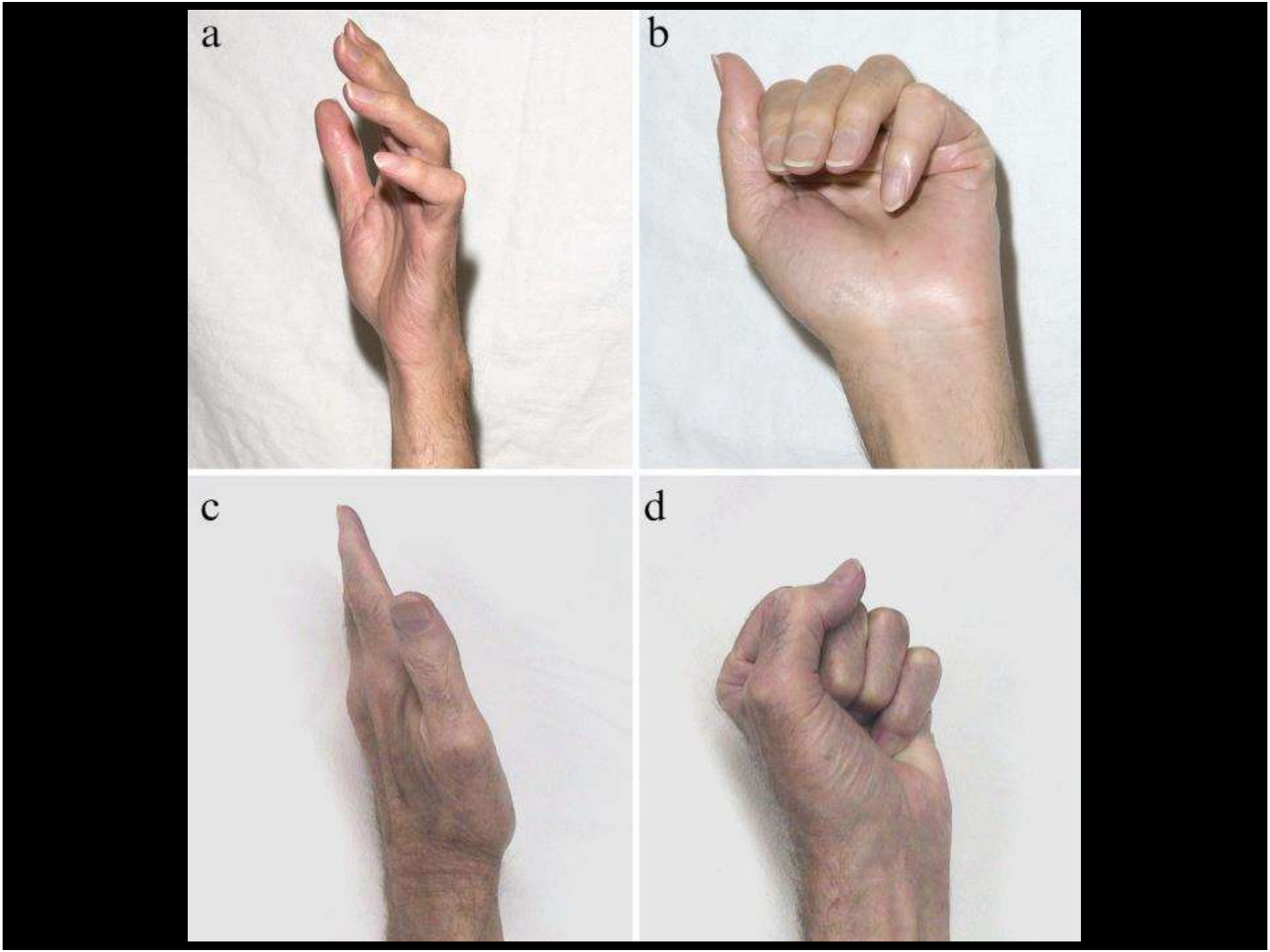


CD34 (progenitor cells)



Case 12

- Pathology:
  - sheets of basophilic cells with diffuse granular chromatin
  - reactive to CD45, CD33, CD34, myeloperoxidase and lysozyme
- Diagnosis: granulocytic sarcoma (myeloid tumor), a focal form of AML
- Treatment: radiation, systemic chemotherapy and intrathecal methotrexate


a
b
c
d

Results of Targeted Fascicular Biopsy Nerve Biopsy Diagnoses (n=138)

- Malignancies & Masses 50
  - perineurioma 15
  - lymphoma 12
  - metastatic breast 8
  - injury neuroma/regeneration 4
  - metastatic prostate 2
  - amyloidoma 2
  - schwannoma 2
  - inflammatory pseudotumor 1
  - neurofibroma 1
  - leptomeningial astrocytoma 1
  - glomangioma 1
  - myeloid tumor 1

Results (cont.)
Nerve Biopsy Diagnoses (n=138)

• Inflammatory	57	
– Demyelination		42
– Vasculitic		12
– Granuloma/sarcoid		2
– Other		1
• Vascular Malformation	4	
– Angiofibrolipomatous hamartoma		3
– Hemangiomatosis		1
• Radiation Injury	2	
• Infectious/Leprosy	1	
• Inherited/HNPP	1	
• Non-diagnostic	23	
– Inflammatory		9
– Non-inflammatory		14

Nerve Biopsy Results

	N	Important changes	Non-diagnostic
Distal cutaneous	30	10 (33%)	20 (67%)
Proximal fascicular, proximal cutaneous and root	130	109 (84%)	21 (16%)

$p<0.0001$

- In highly selected cases, proximal fascicular biopsies were more likely to show diagnostic or meaningful pathology than distal cutaneous biopsies.

Nerve Biopsy Results

- 85 of the 115 diagnostic cases (74%) had potentially treatable conditions.
- Proximal fascicular biopsies often caused mild transient neurological side effects (numbness, pain and new weakness).
- Few symptoms or deficits persisted.

Fascicular Biopsy Conclusions

1. In carefully selected cases, proximal biopsies at sites of imaging abnormality provide specific diagnostic information not identified in distal nerve.
2. Despite being invasive, proximal fascicular biopsies may be justified because of therapeutic implications.
3. Because of potential morbidity, proximal nerve biopsy should only be performed in medical centers with special expertise in:
   - neuropathy patient care
   - peripheral nerve imaging
   - nerve surgery
   - nerve pathology

Overall Conclusions

1. Although most patients with neuropathy should not have nerve biopsies, they are still very useful in diagnosing and in directing therapy in selected cases.

2. Nerve biopsy is still the only way to view the interstitium and the interstitial abnormalities are the most important information gained from nerve biopsy.

Overall Conclusions

3. When deciding to do a nerve biopsy consideration should be given to what nerve is biopsied, what type of biopsy should be done (whole or fascicular), what are the likely diagnoses and how likely are the nerve biopsy results to change the patient's management.

4. Nerve biopsies should be taken from nerves that are clinically involved by the disease process.

Overall Conclusions

5. MRIs are useful in evaluations of focal, motor and proximal neuropathies.

6. The use of targeted fascicular nerve biopsy from proximal MRI lesions has expanded the use of nerve biopsy and has allowed diagnosis and treatment of patients who would have previously been undiagnosed.

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