Peripheral Nerve Biopsies

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Disclosures

- I have the following relevant financial relationships to disclose
  - Nature of the relationship
    - Advisory board meeting, Servier Pharmaceuticals

Learning Objectives

At the end of this activity learners should be able to:

- Outline common reasons / indications for clinicians to order a peripheral nerve biopsy
- Explain histopathologic features pointing towards a diagnosis of peripheral nerve involvement by vasculitis
- Identify features that could point towards an unusual etiology for peripheral neuropathy in a nerve biopsy

AANP

Peripheral neuropathy – Clinical Side

- 1% to 2% of the population affected, 7% to 8% of the elderly
- Many patients just seen by the PCP
- Common etiologies: Diabetes, alcohol, drug toxicity

- History, Hb A1c, B12, metabolic panel, TSH, SPEP

=> Atypical features => neurologist

=> A small selection needs a nerve biopsy

Common Clinical Indications for Nerve Biopsies

- Progressive, cryptogenic polyneuropathy.

- Suspected vasculitis, chronic inflammatory process, infection, amyloidosis.

Common Findings in / Diagnoses on Nerve Biopsies

Common descriptive findings (1):

- Axonal loss (79%)
- Wallerian degeneration (38%)
- Vasculitis (9%)
- Amyloid (3%)
- Vessel instead of nerve (up to 4% (?))
- Lymphoma 0.3%
- Normal (17%)

Specific diagnoses affected treatment in about a quarter to a third (1, 2):
Confirmed

- Suspected vasculitis in 60%
- Suspected amyloid in 40%

1: PMID: 32560468 2: PMID: 33629393

AANP

Special stains and studies – No uniformly adopted protocol

Journal of the Peripheral Nervous System 15:164–175 (2010)

PNS NERVE BIOPSY GUIDELINE

Peripheral Nerve Society Guideline on processing and evaluation of nerve biopsies

Claudia L. Sommer, Germany; Sebastian Brandner, United Kingdom; Peter J. Dyck, USA; Yadollah Harati, USA; Catherine LaCroix, France; Martin Lammens, The Netherlands; Laurent Magy, France; Svein I. Mellgren, Norway; Michela Morbin, Italy; Carmen Navarro, Spain; Henry C. Powell, USA; Angelo E. Schenone, Italy; Ersin Tan, Turkey; Andoni Urtizberea, ENMC; Joachim Weis, Germany

"Very little high-quality evidence is available for the usefulness of specific methods in nerve biopsy work-up and evaluation. This is contrast to a large body of expert opinions and experience"

PMID: 21040138

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Special stains and studies – No uniformly adopted protocol

- H&E sections (and deeper levels as appropriate)
  - Question of orientation…
- Congo red stain
- Epon sections

- CD3
- CD68
- Trichrome stain

- Sometimes added:
  - EM
  - Other IHC stains

- Not done: IF, teased fiber preparations

Some general comments

- Specimen appropriate
  - Histology matching anatomic location?
  - Long enough? Well enough preserved?
- Inflammation?
- Vascular changes?
- Amyloid?
- Epon sections:
  - Expected density of large myelinated axons?
  - Uniform distribution?
  - Myelin thickness appropriate for diameter of axons?
  - Onion bulbs?
  - Any infiltrates?

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Case 1

Clinical history:

69-year-old with bilateral foot pain (6 out of 10; dull, achy)

Pain developed over 5 weeks and associated with numbness

Patient’s ability to walk / exercise is affected

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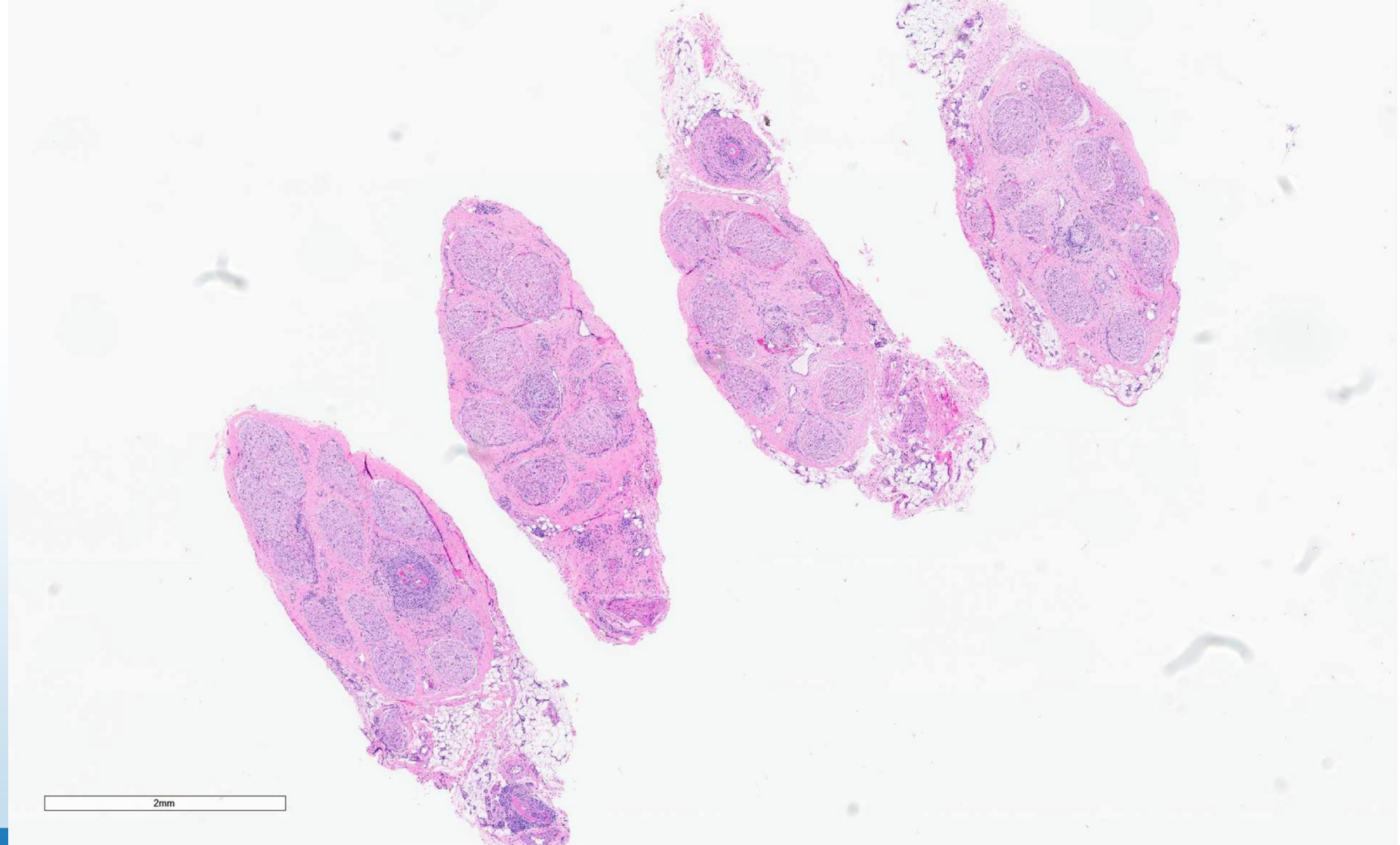
Pain developed over 5 weeks and associated with numbness

Patient's ability to walk / exercise is affected

Of note: symptoms started after several cycles of immunotherapy for mesothelioma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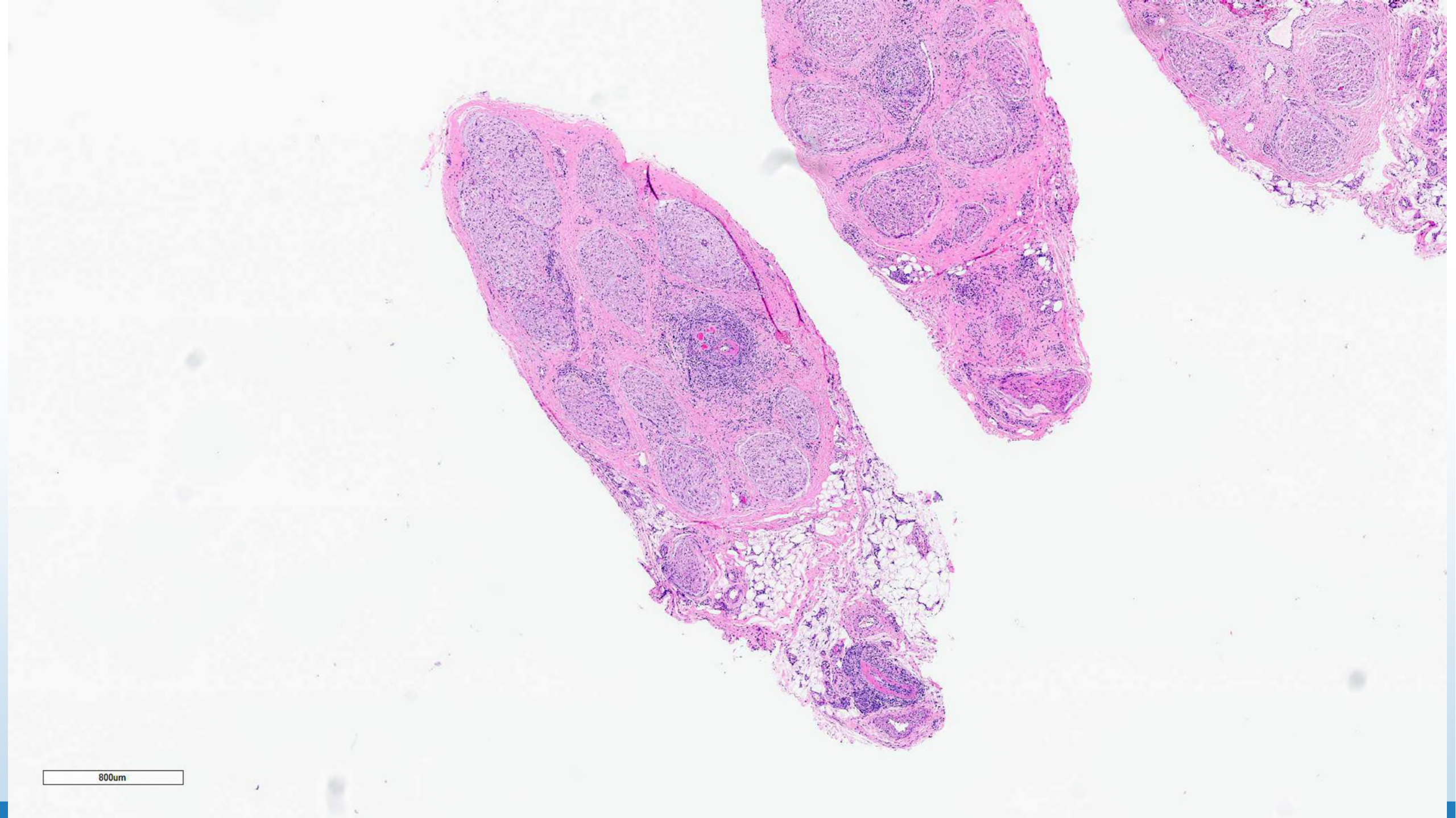
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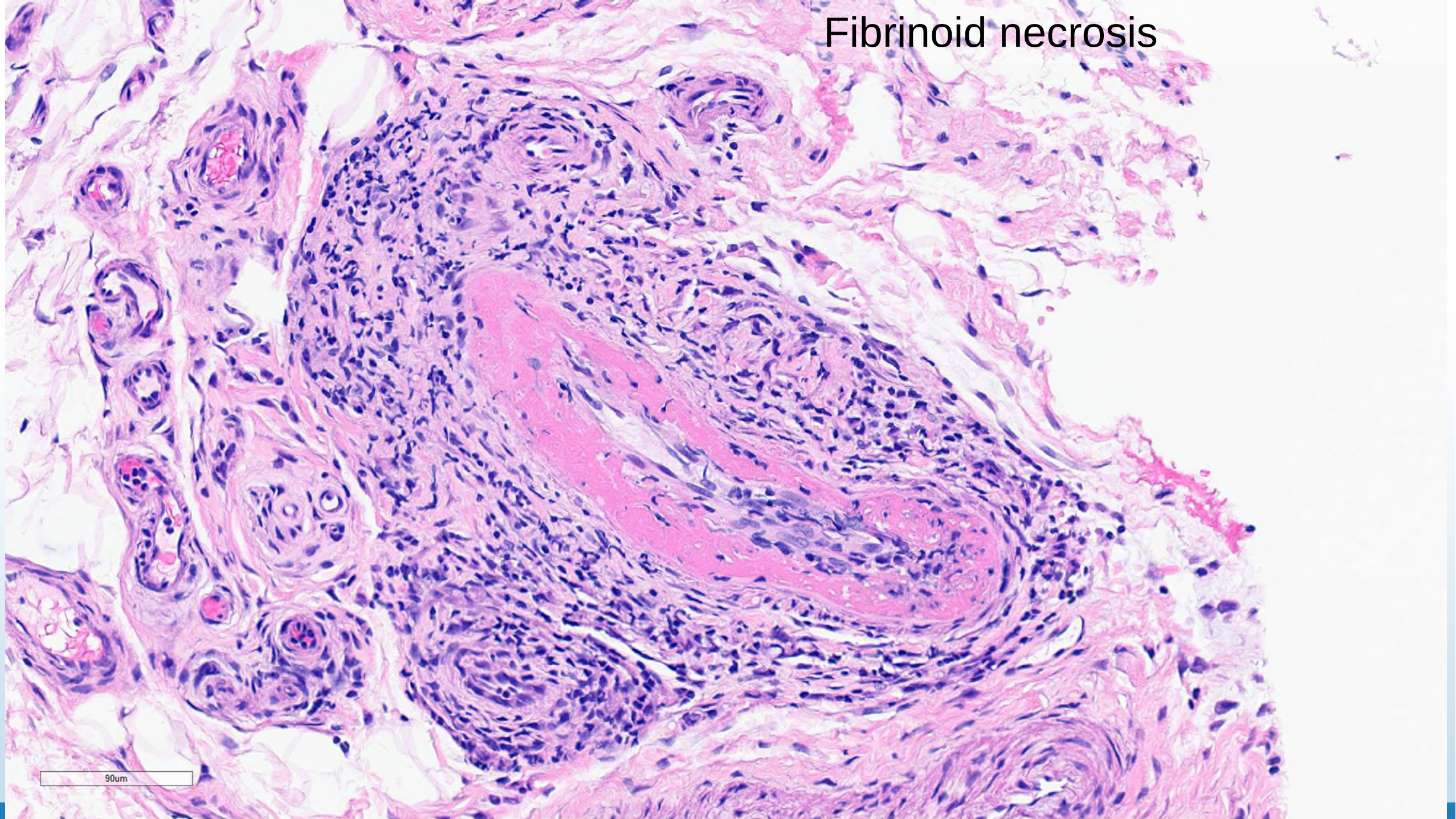
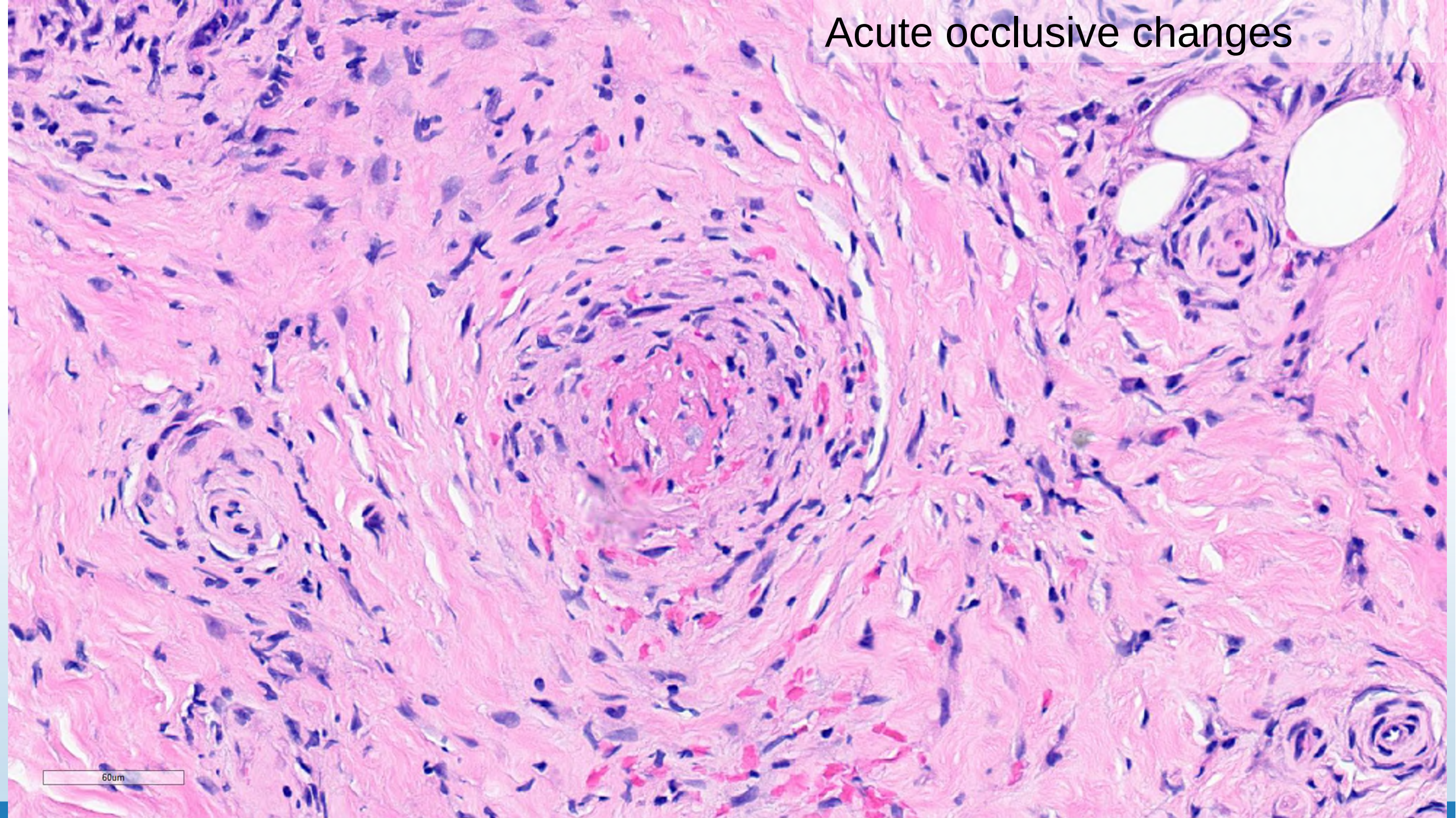
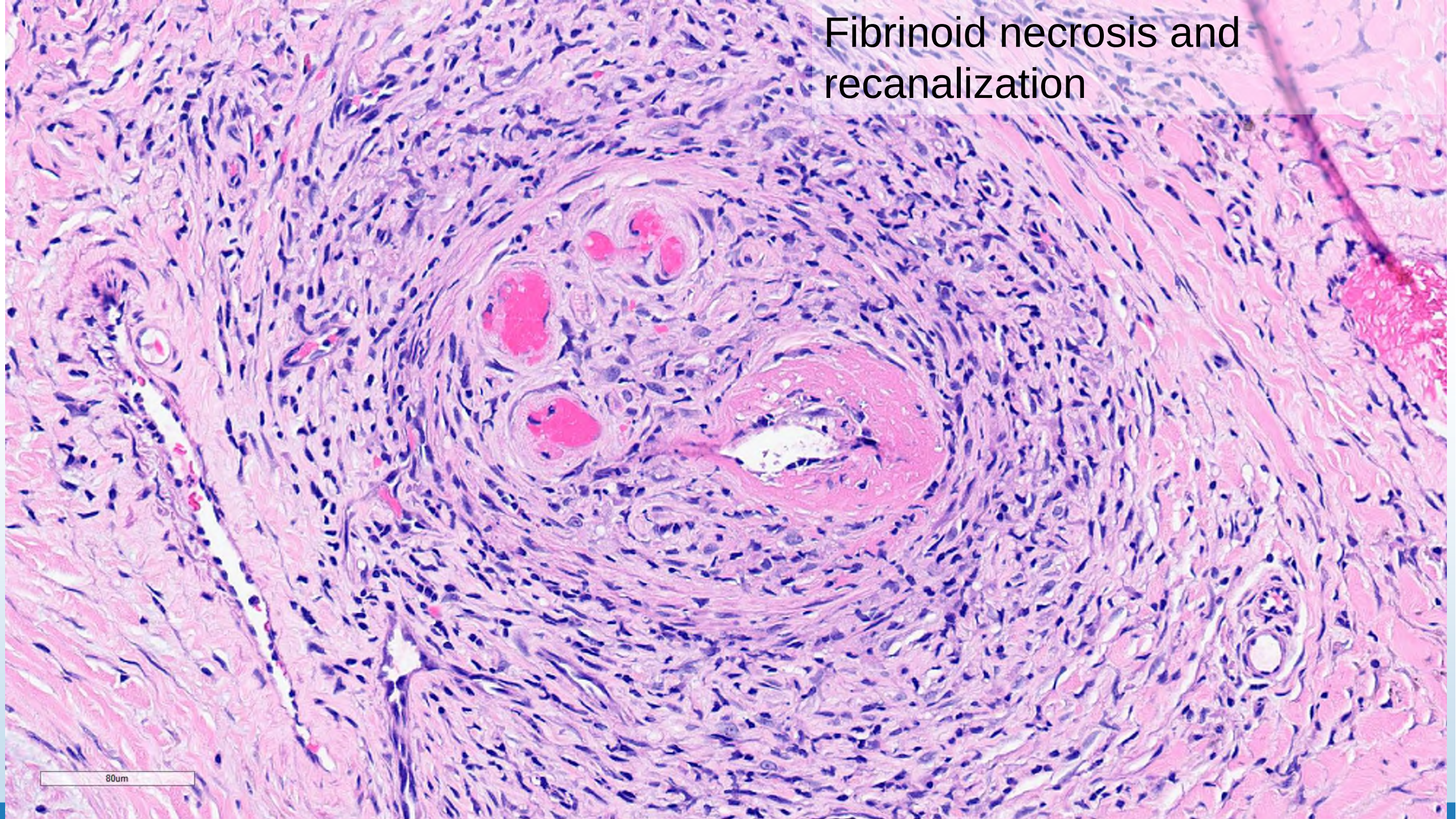
Fibrinoid necrosis



Acute occlusive changes




Fibrinoid necrosis and recanalization
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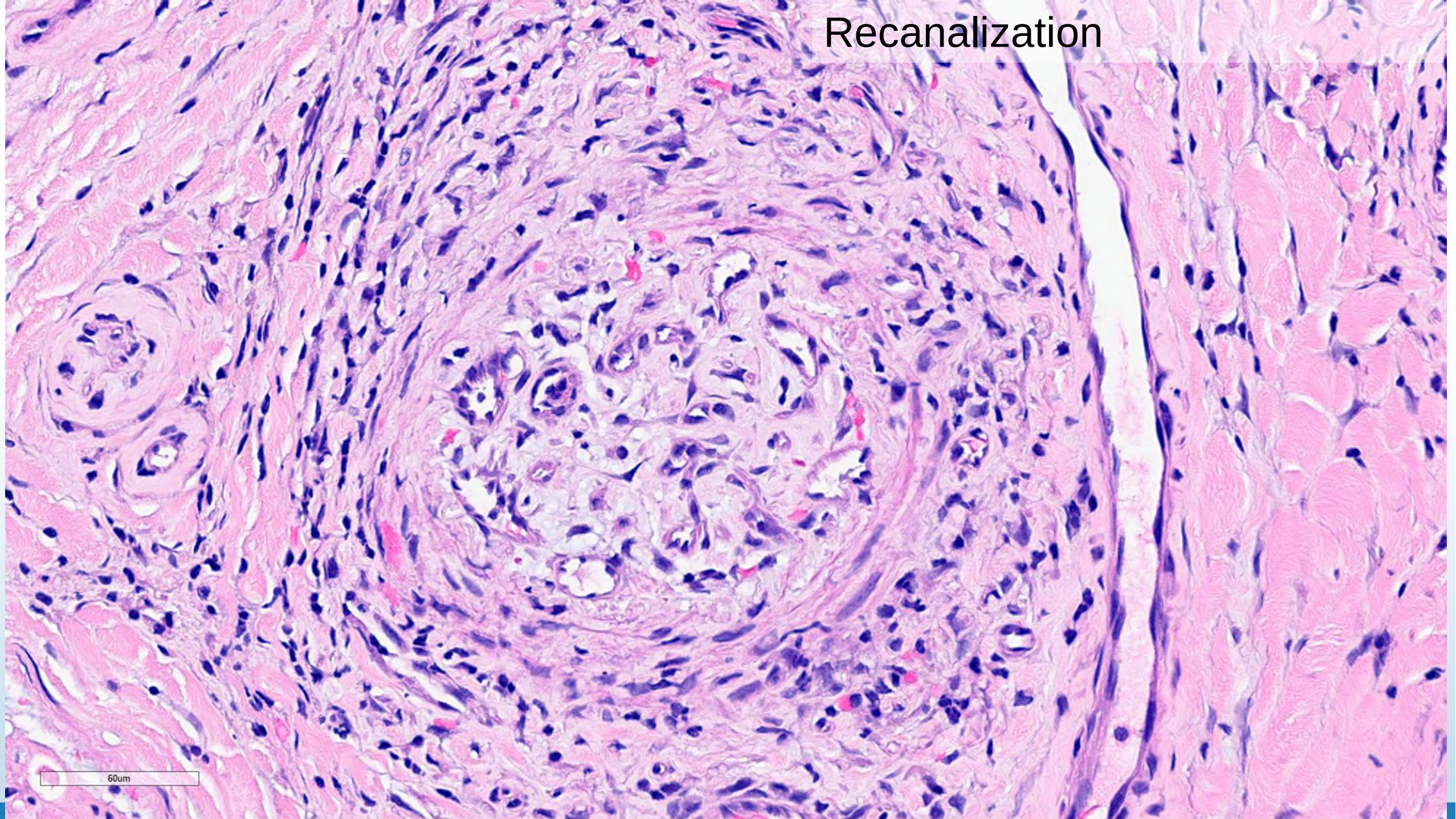
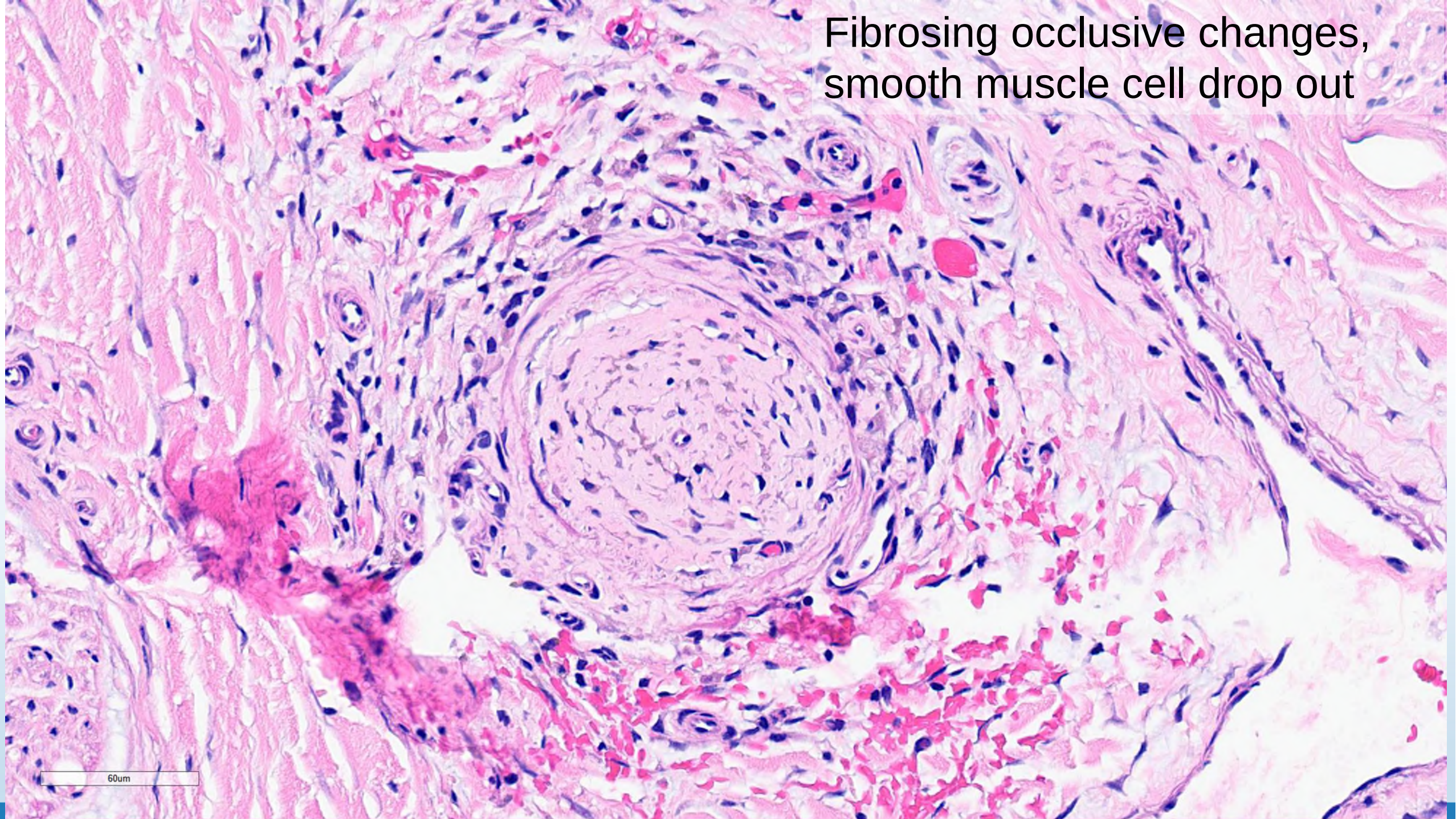
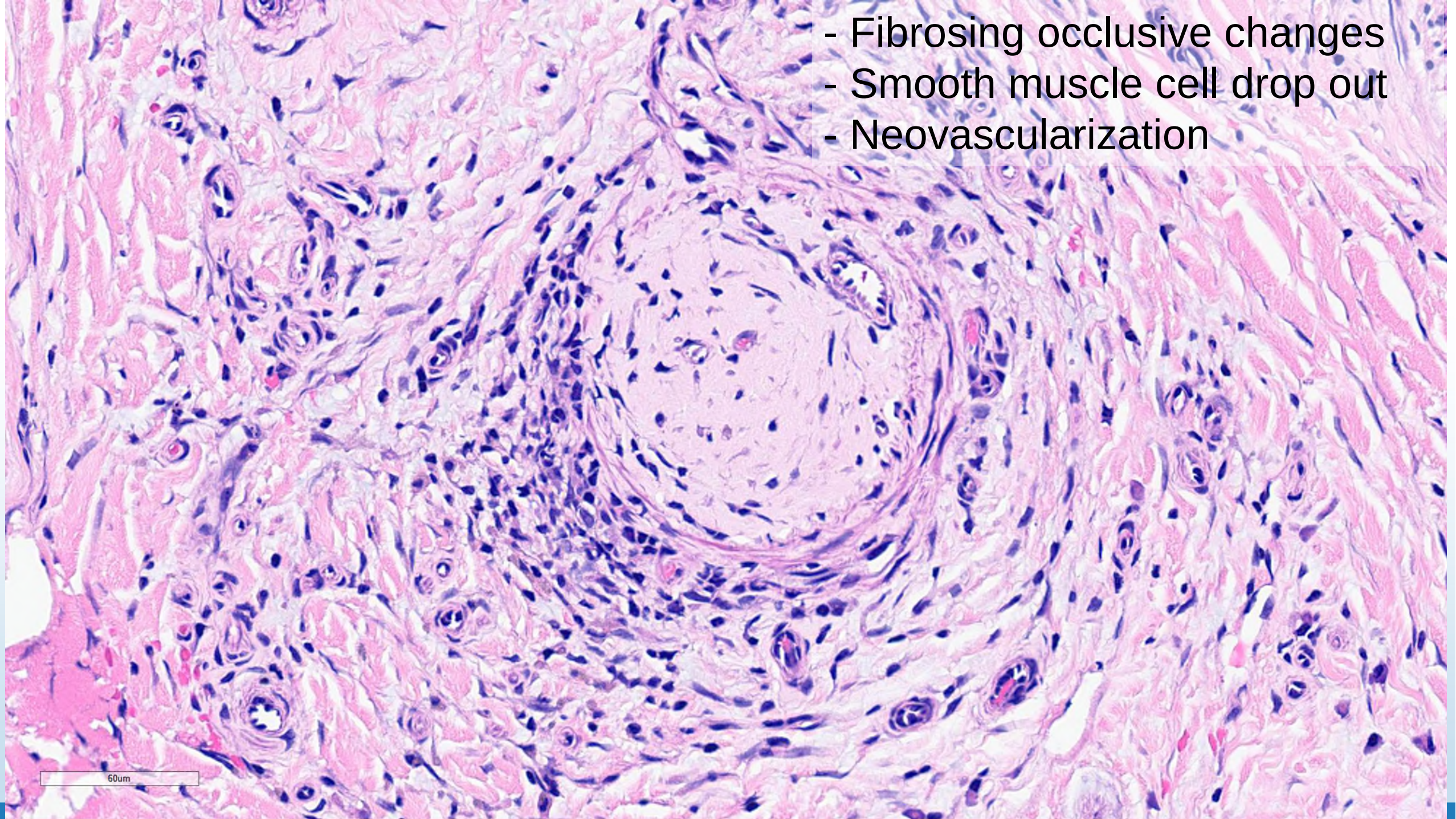
Recanalization




Fibrosing occlusive changes,
smooth muscle cell drop out
60um


- Fibrosing occlusive changes
- Smooth muscle cell drop out
- Neovascularization
60um

Case 1

Diagnosis:

Active vasculitis

Comment:

- Affects vessels from 50 to 300microns
- No distinct granulomatous features, not prominent eosinophils
- Congo red negative, Epon sections pending

=> Immediate call to the clinical team

=> Clinical context suggests secondary systemic vasculitis in the setting of immunotherapy

Large vessels in the nerve are small vessels in the vasculitis world

Nerve vasculitis based on the size of the affected vessels:

- Larger epineurial arterioles (75 to 300microns)
  - Mostly systemic vasculitis
    - Primary
      - Polyarteritis nodosa (PAN)
      - Granulomatosis with polyangiitis (GPA; formerly Wegener)
      - Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg Strauss)
      - Immune complex associated cryoglobulinemic vasculitis
    - Secondary systemic vasculitis (drugs, paraneoplastic, etc.)
- Microvessels (typically less than 40microns; small arterioles, endoneurial microvessels, capillaries, venules)
  - Mostly nonsystemic vasculitic neuropathy (NSVN)

AANP

Typical clinical features

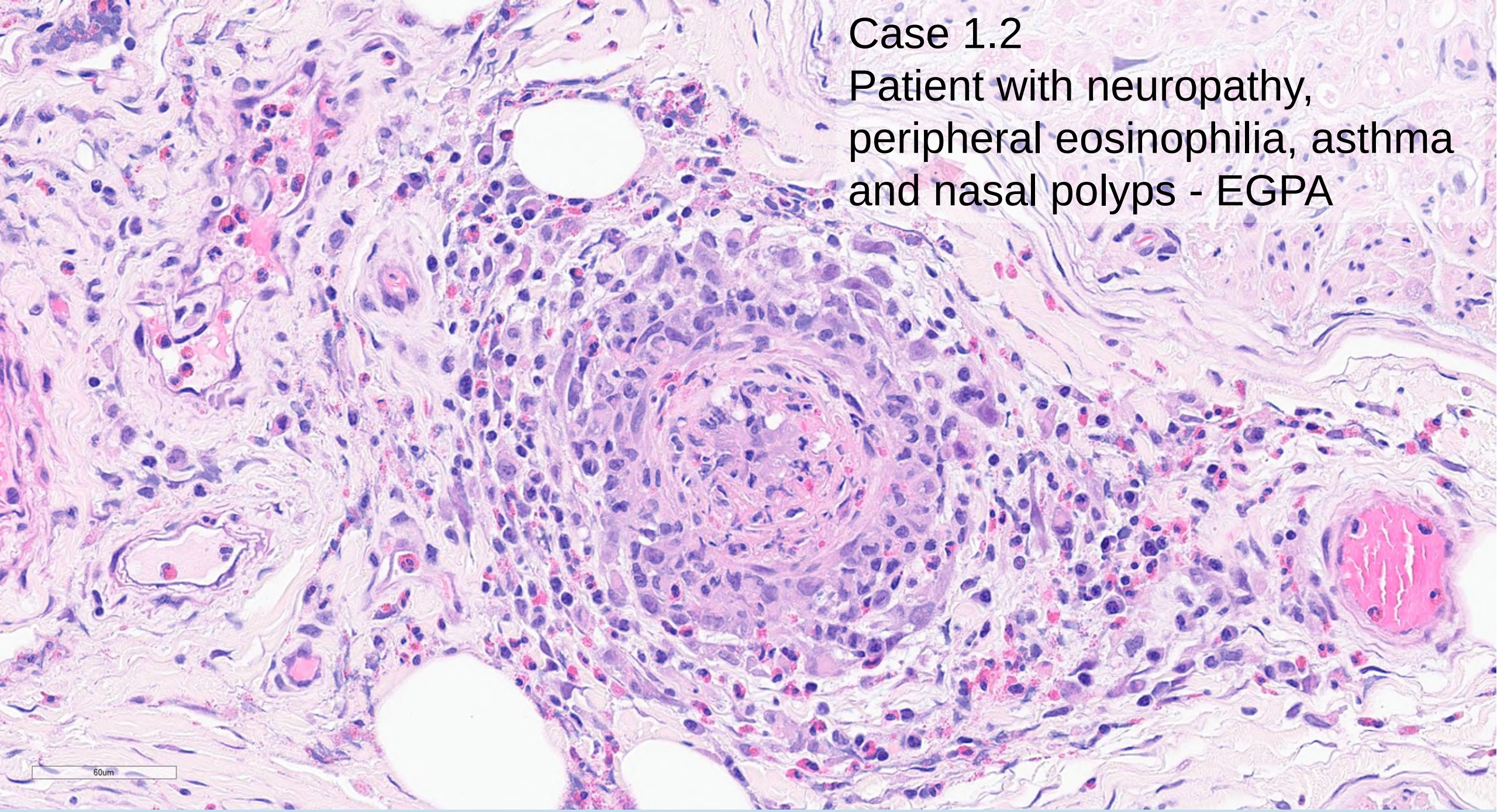
- Painful sensory or mixed sensory / motor neuropathy
- Acute or subacute
- Individual nerves sequentially affected (“mononeuritis multiplex”)

- Systemic vasculitis:
  - Tends to be more fulminant / acute
  - Features of organ involvement (rash, GI symptoms, respiratory problems, hematuria)
  - Constitutional symptoms like fever, chills, night sweats, weight loss

AANP

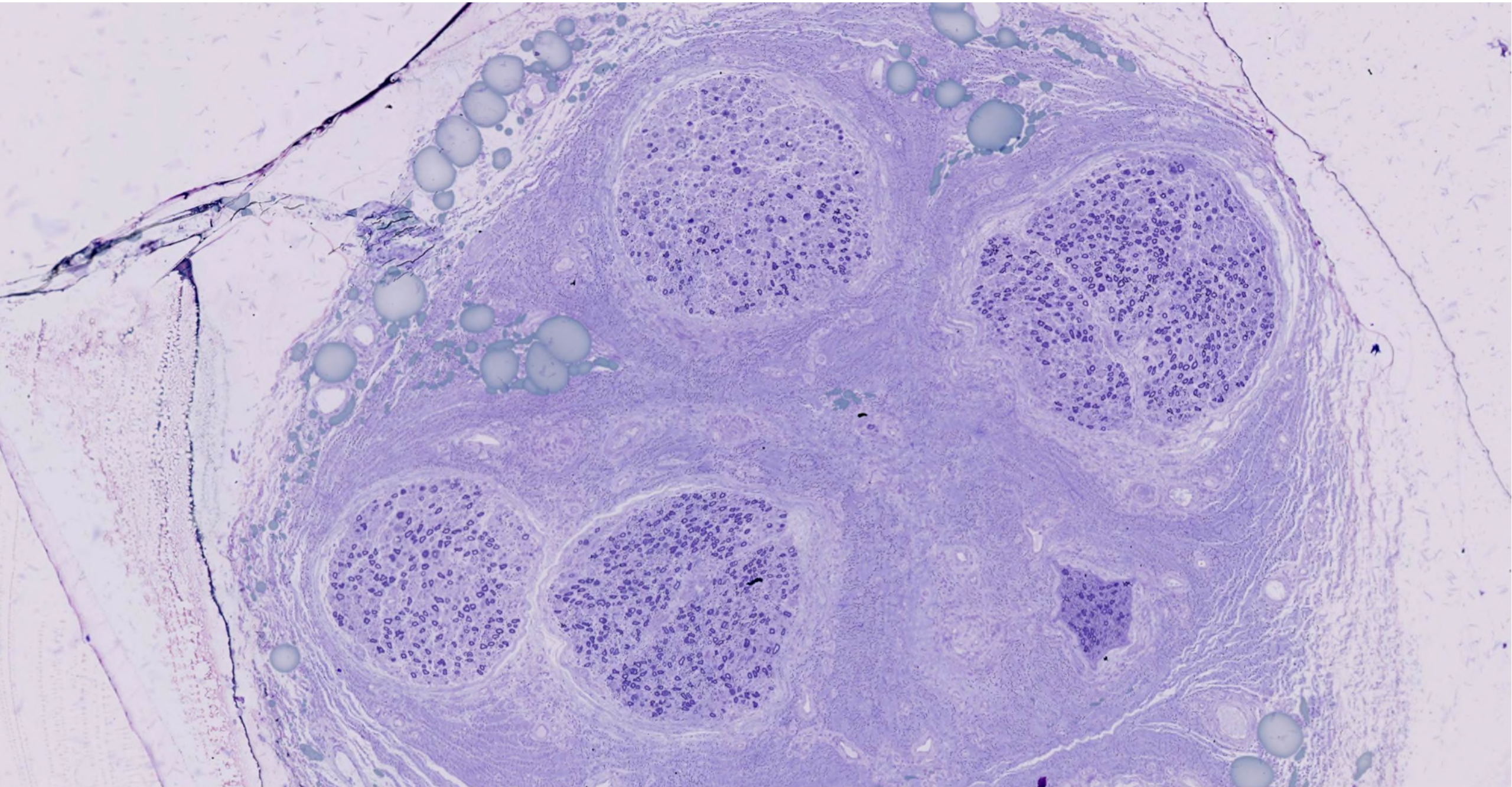
General laboratory test results to look for

- CBC, metabolic panel
- ESR, CRP
- ANA, rheumatoid factor, hepatitis B/C, cryoglobulins
- ANCA
  - c-ANCA (PR3-ANCA) associated with granulomatosis with polyangiitis
  - p-ANCA (MPO-ANCA) associated with eosinophilic polyangiitis and microscopic polyangiitis



Case 1.2
Patient with neuropathy, peripheral eosinophilia, asthma and nasal polyps - EGPA

Asymmetric loss of large axons

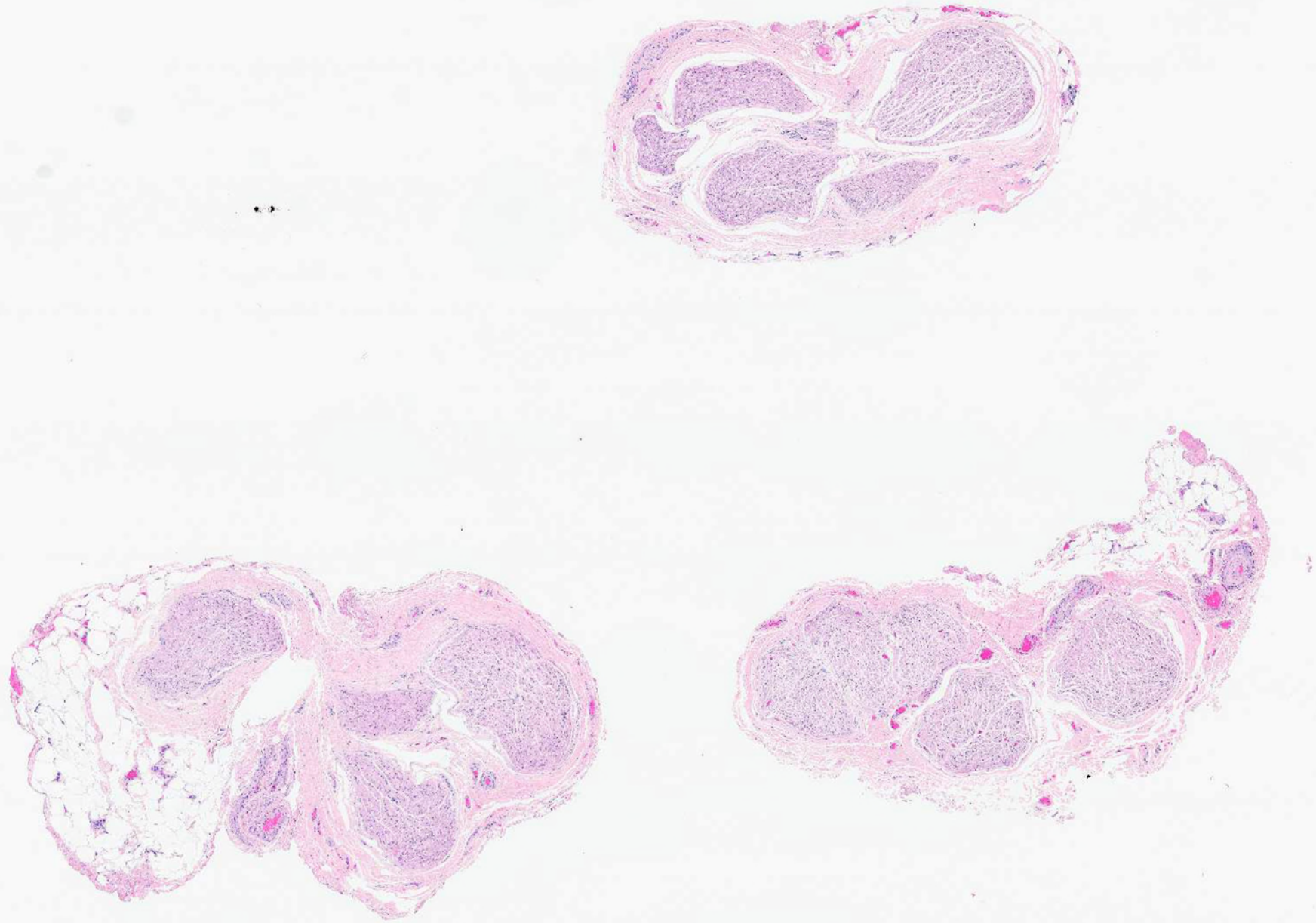


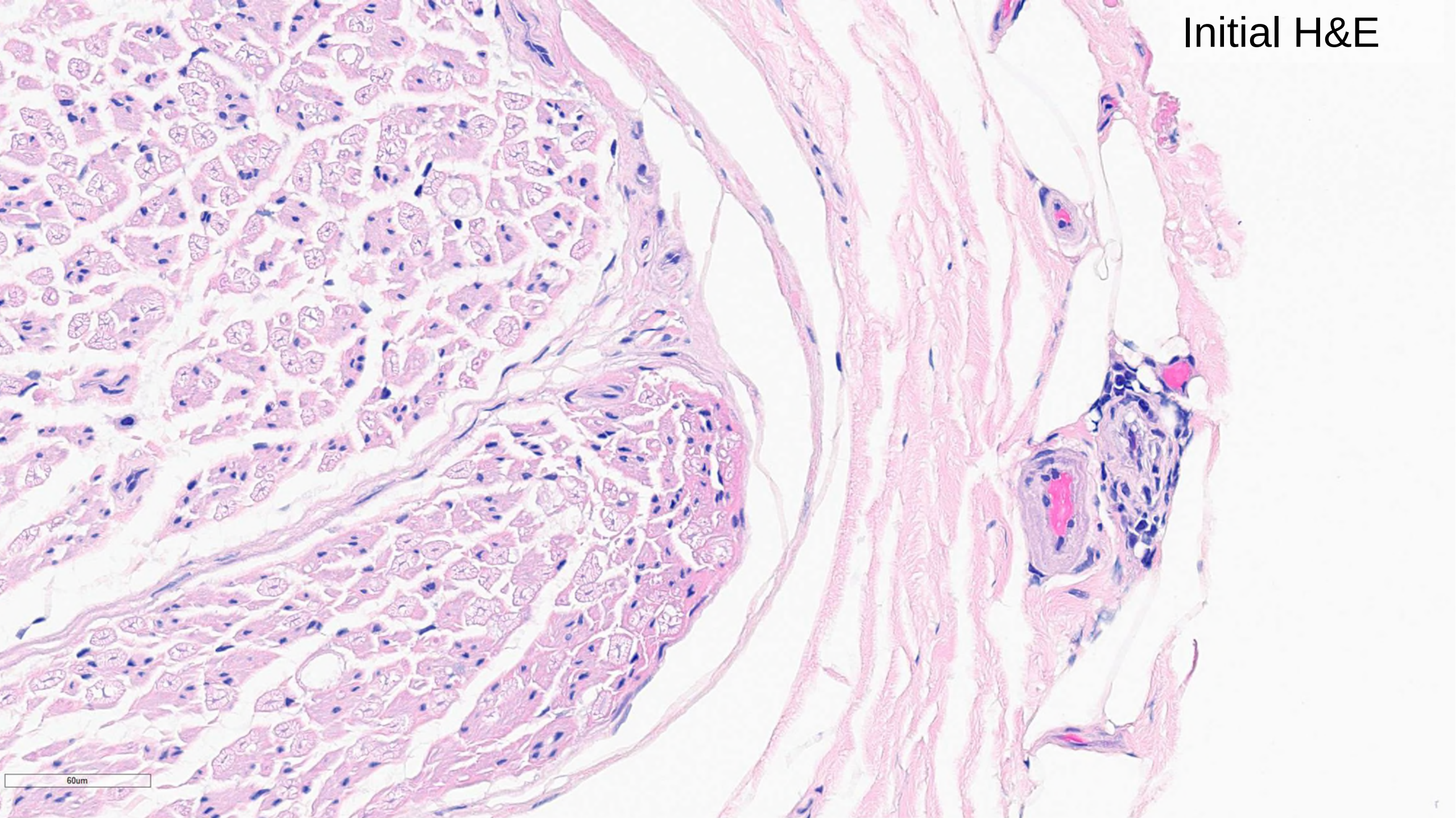
Case 2

Clinical history:

59-year-old with weakness

Initial H&E




Initial H&E
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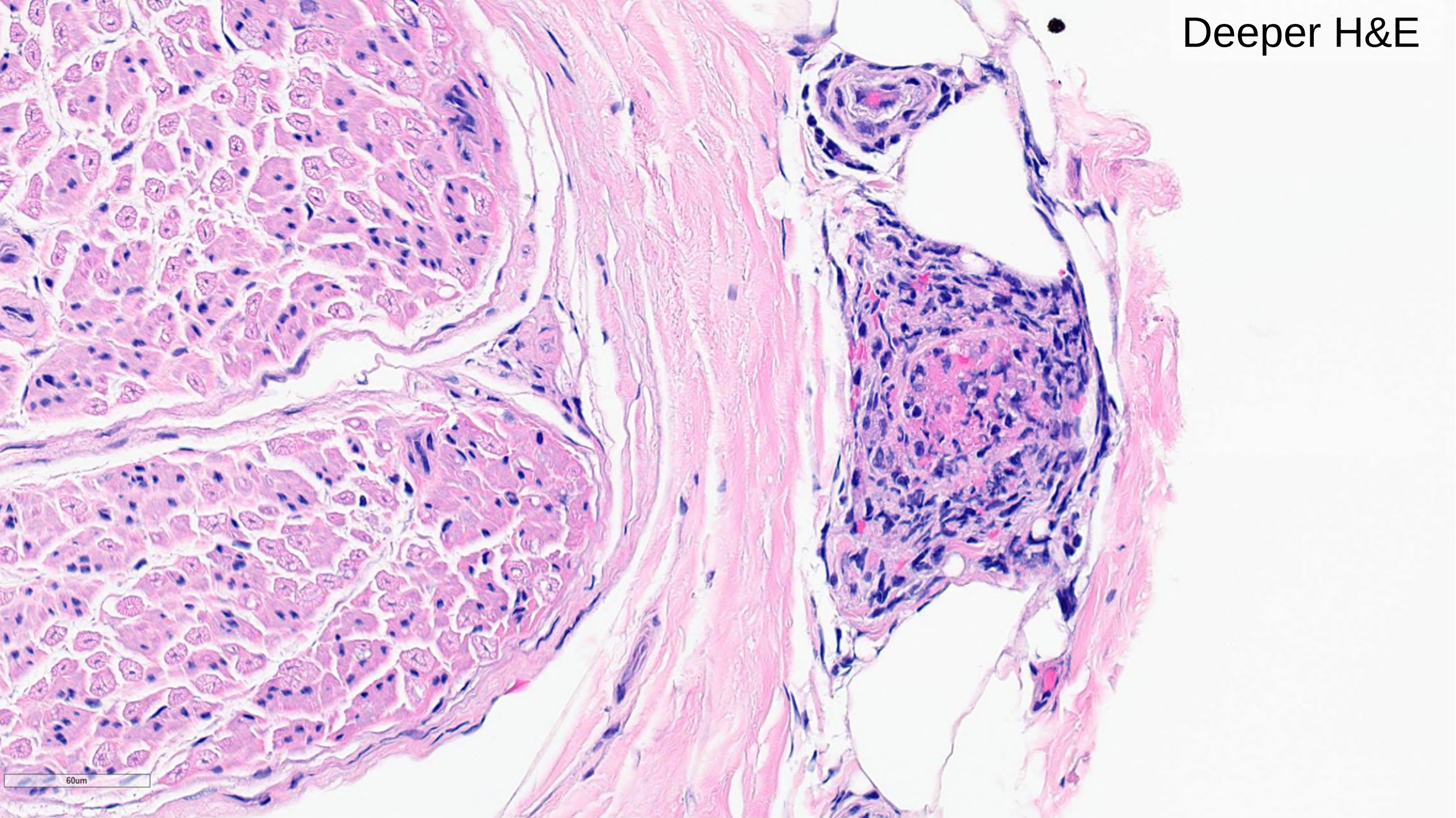

Deeper H&E
60um

Case 2

Diagnosis:

Active vasculitis affecting small vessels

=> Possible nonsystemic vasculitic neuropathy (NSVN)

My favorite special stain for nerve biopsies?

- Deeper levels x3

Diagnostic Criteria for Vasculitis

I. Active lesion:

- Inflammation in the wall and
- Acute wall damage (fibrinoid necrosis; loss / disruption of endothelium; loss / fragmentation of internal elastic lamina; loss / fragmentation of smooth muscle cell layer; thrombosis)

II. Chronic lesion:

- Inflammation in the wall and
- Chronic vascular damage (intimal hyperplasia, fibrosis of the media, adventitial fibrosis, chronic thrombosis with recanalization)

III. No evidence of another primary disease process that can mimic vasculitis (lymphoma, lymphomatoid granulomatosis, amyloid)

1: PMID: 21040139

*Concomitant muscle biopsy may improve yield

Diagnostic Criteria for Probable Vasculitis

I. Predominantly axonal changes AND

II.

(A) *Peri*vascular inflammation with acute or chronic wall injury

OR

(B) Perivascular inflammation plus

- Hemosiderin deposits
- Asymmetric /multifocal axonal loss
- Prominent active axonal loss
- Vascular deposits of complement, IgM, fibrinogen by IF

1: PMID: 21040139

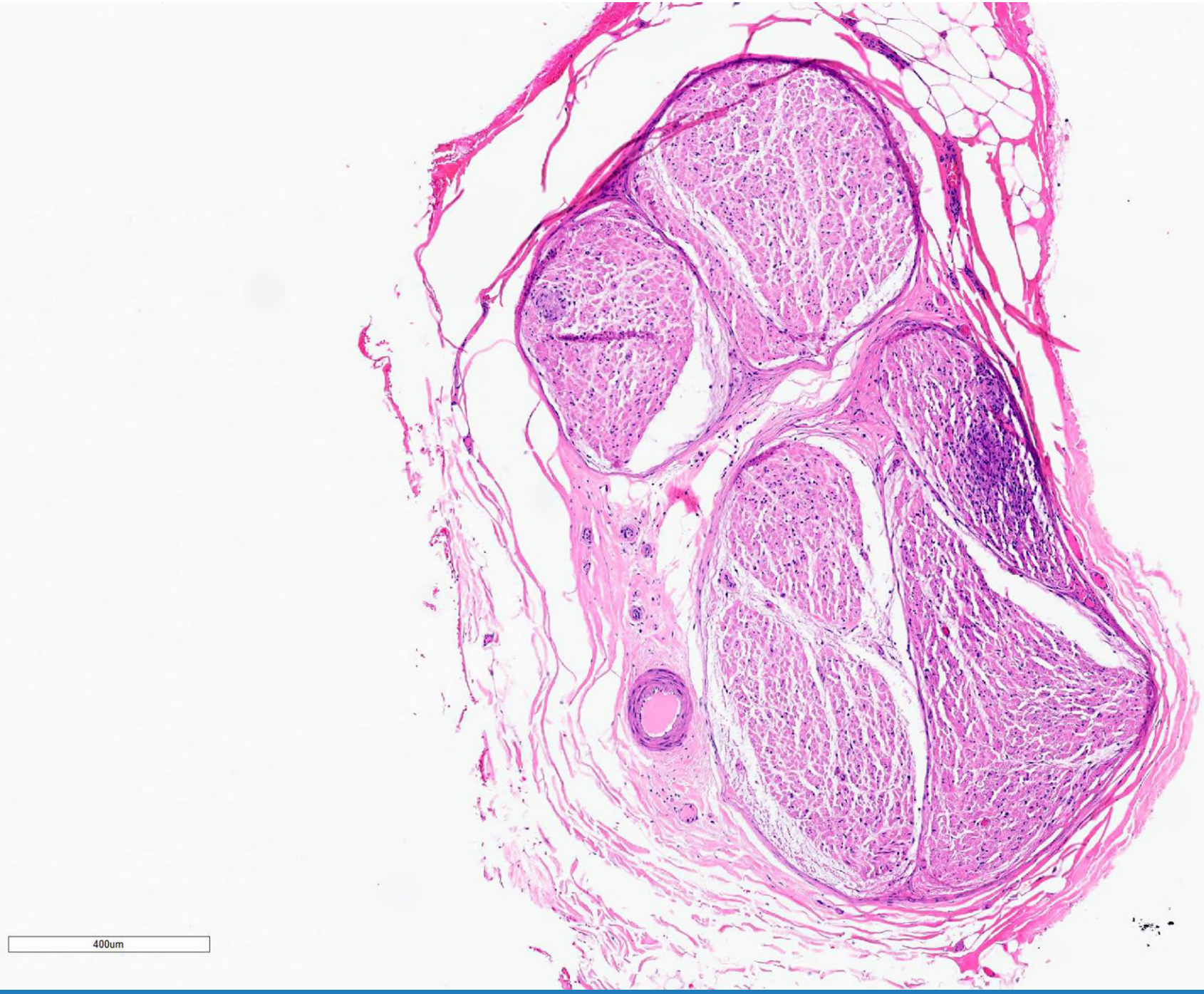
Some pearls

- Deeper levels
- Some preliminary results warrant an early call to the clinicians

Case 3

Clinical history:

- 20-year-old with history of polyneuropathy and myopathy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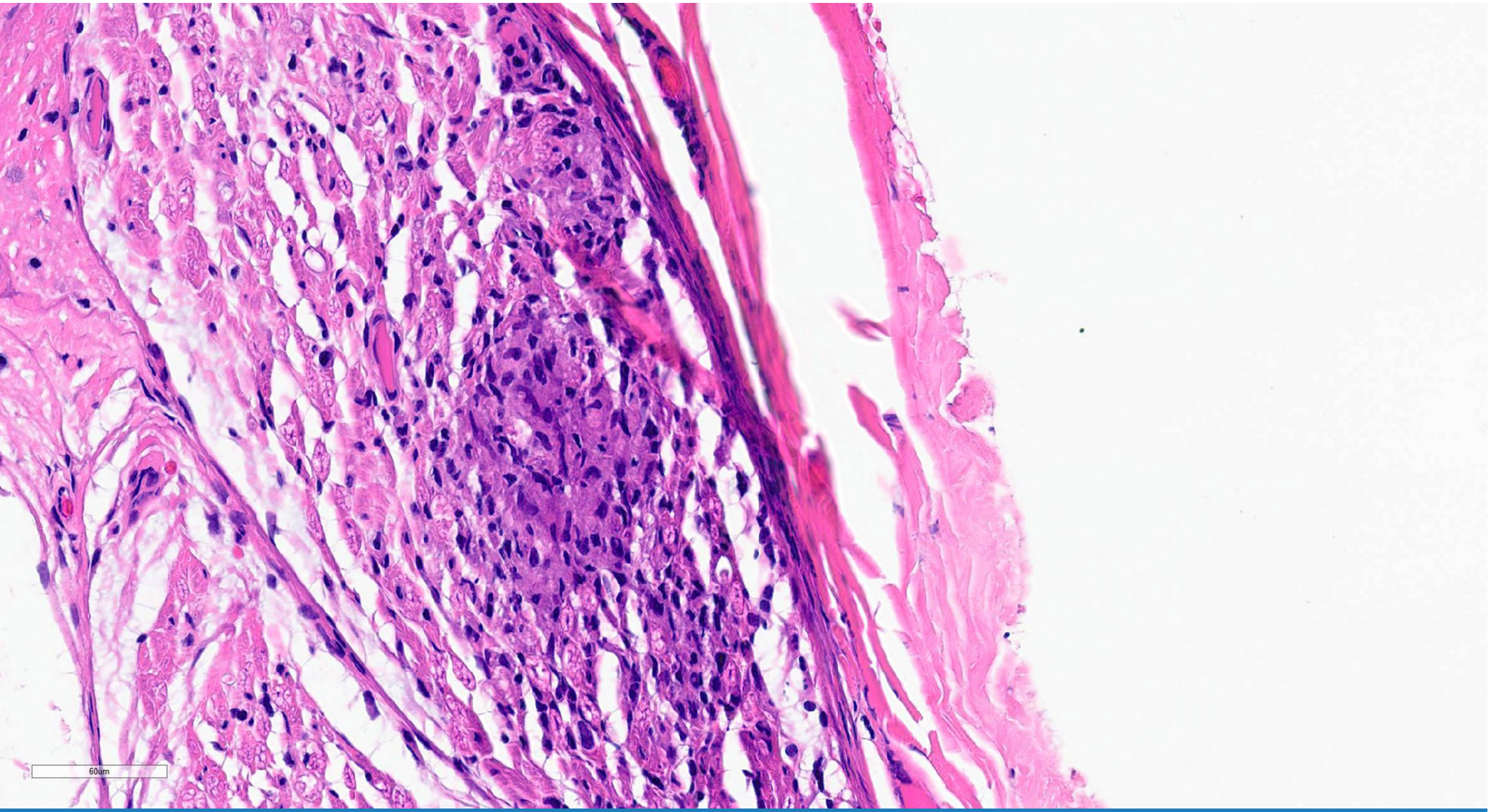
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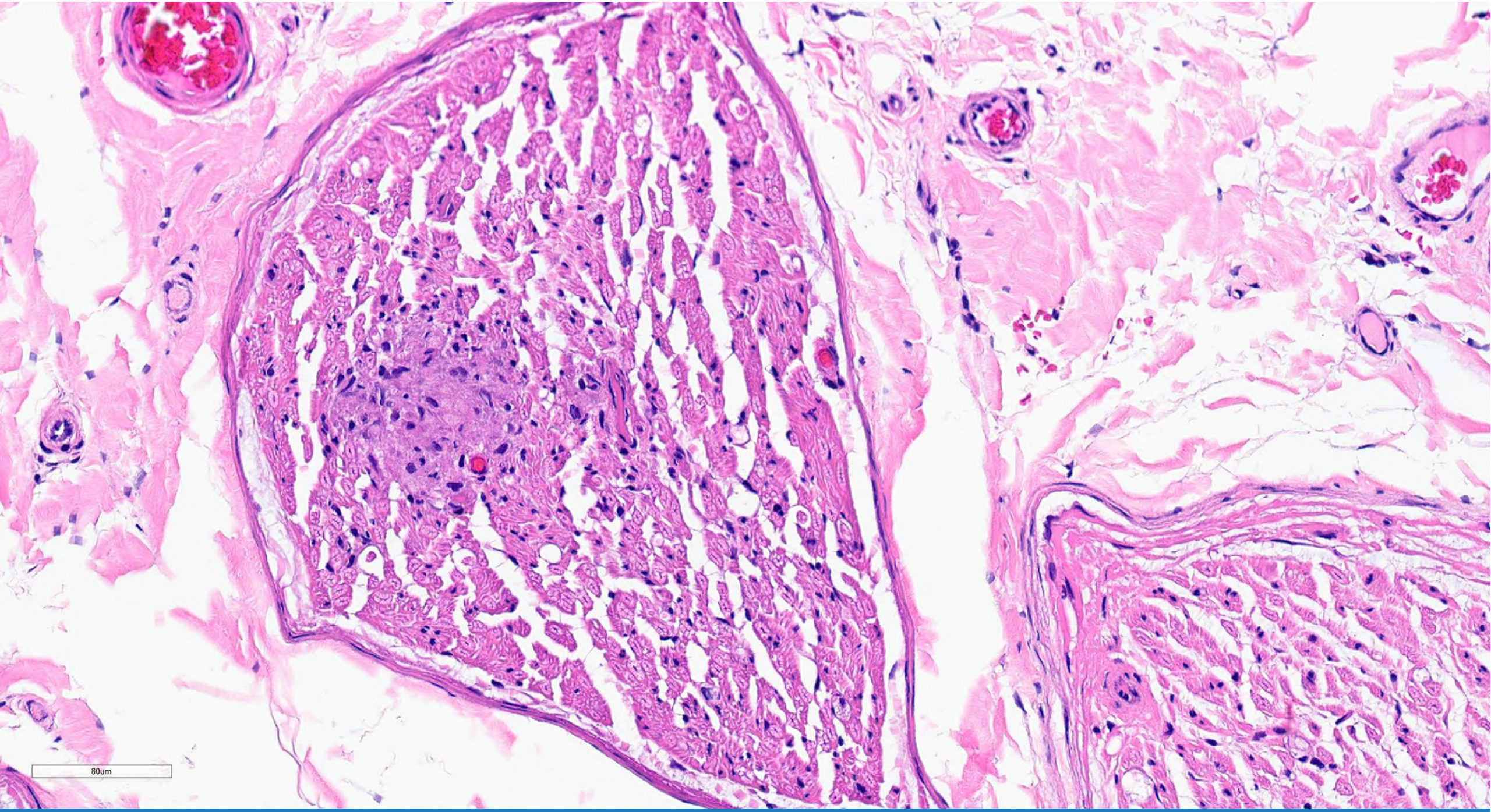
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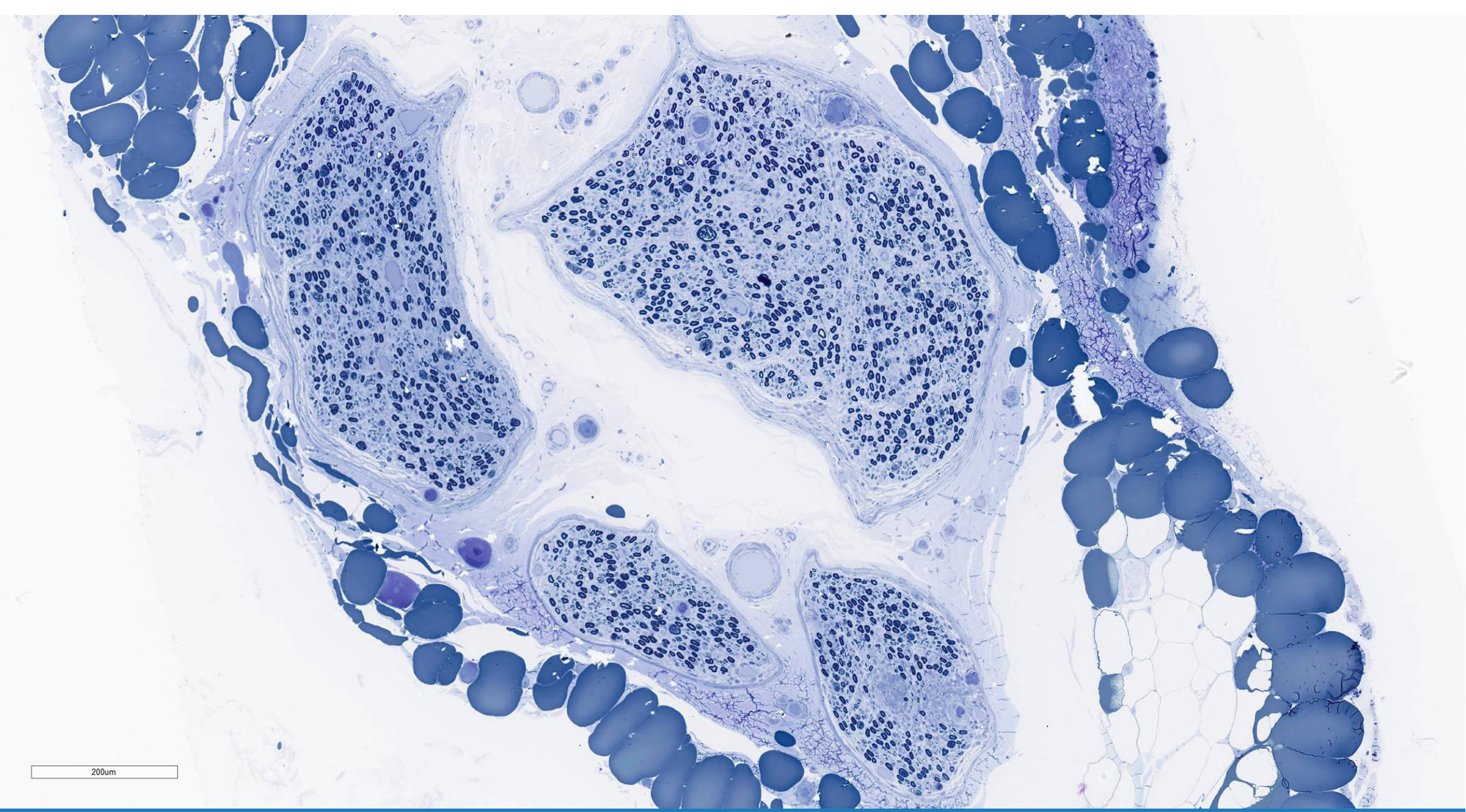
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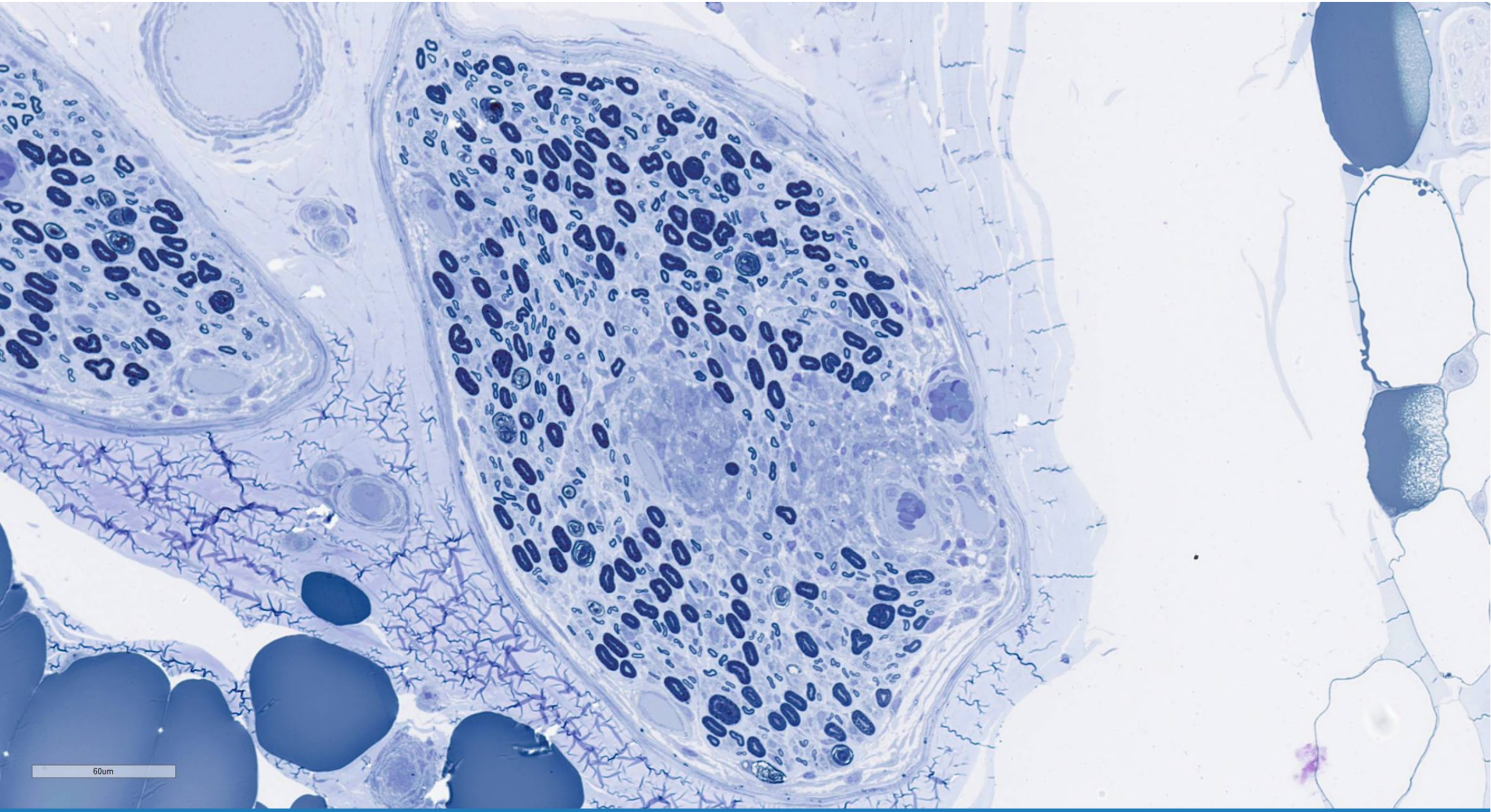
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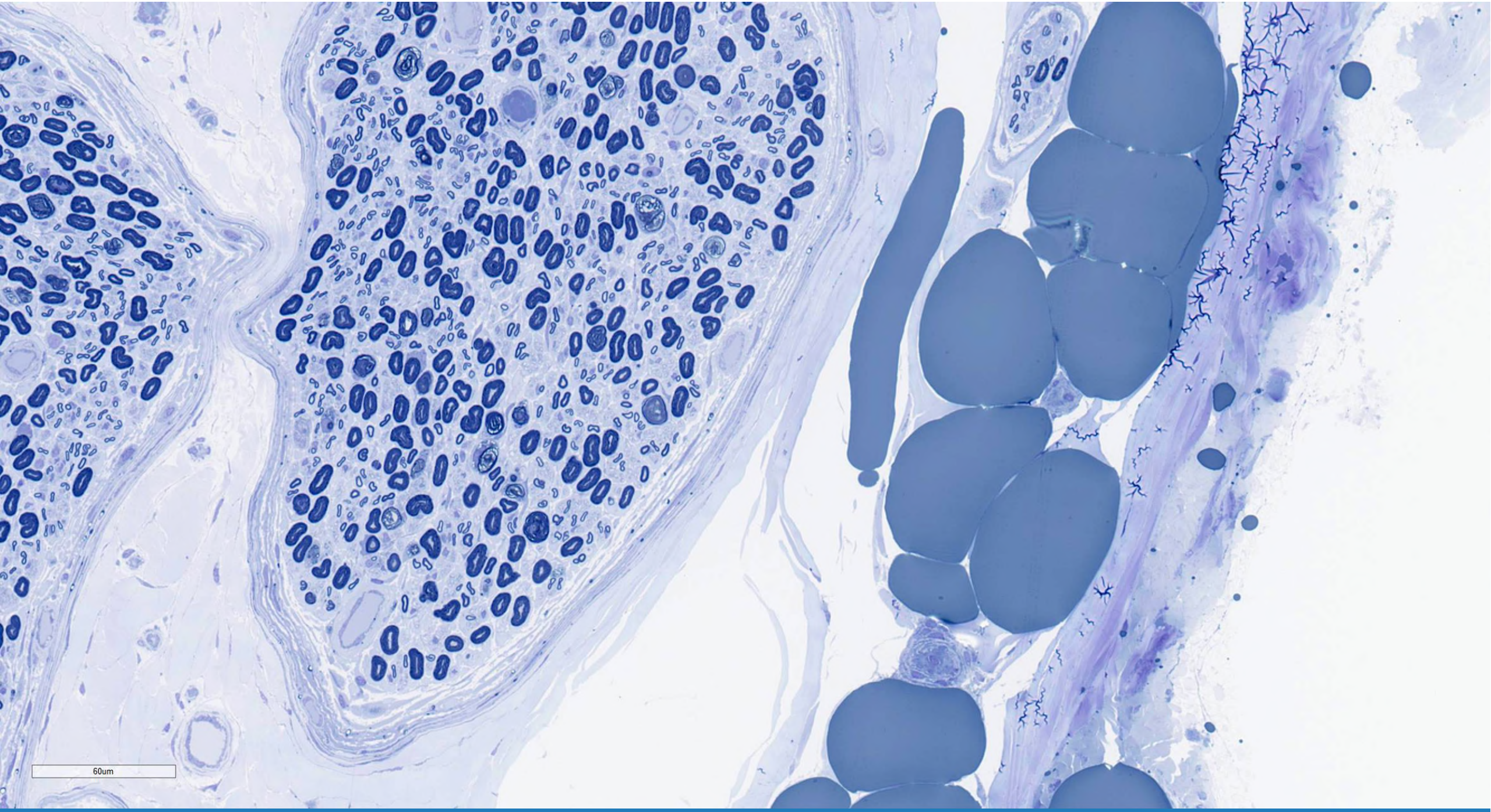
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Case 3

Diagnosis:

- Peripheral nerve (and skeletal muscle) with granulomatous inflammation
- Axonal loss and ongoing axonal degeneration
- AFB and GMS stains negative

=> Findings worrisome for sarcoidosis

Sarcoidosis in peripheral nerve biopsies

- 1% of patients with sarcoidosis have neuropathy
- Sarcoid neuropathy is clinically heterogeneous
- Sarcoid neuropathy can be the initial presentation
- Sometimes associated with vasculitis-like changes

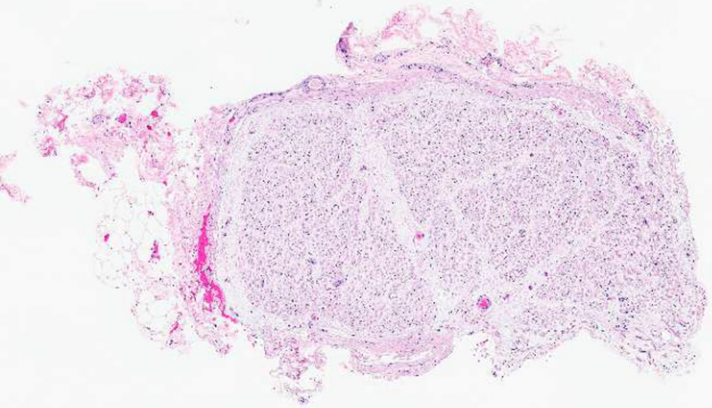
*Concomitant muscle biopsy may improve yield

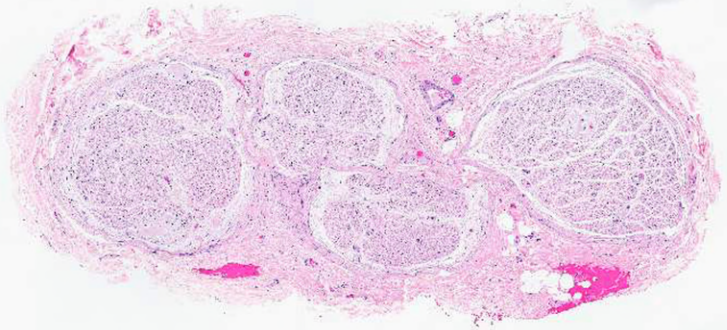
1: PMID: 33629393

Case 4

Clinical history:

- 55-year-old with orthostatic hypotension, nausea, vomiting, and length dependent axonal sensorimotor neuropathy





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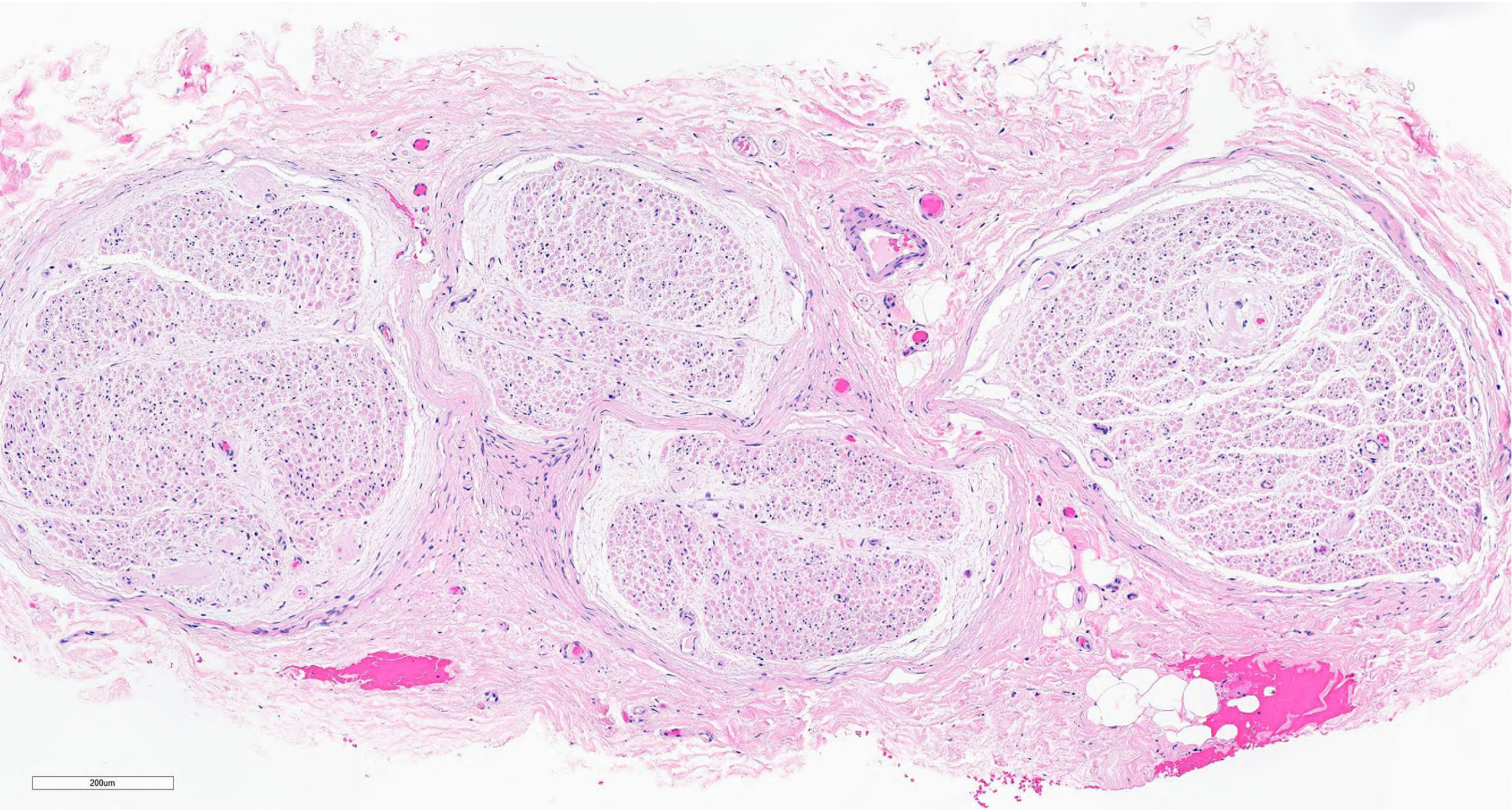
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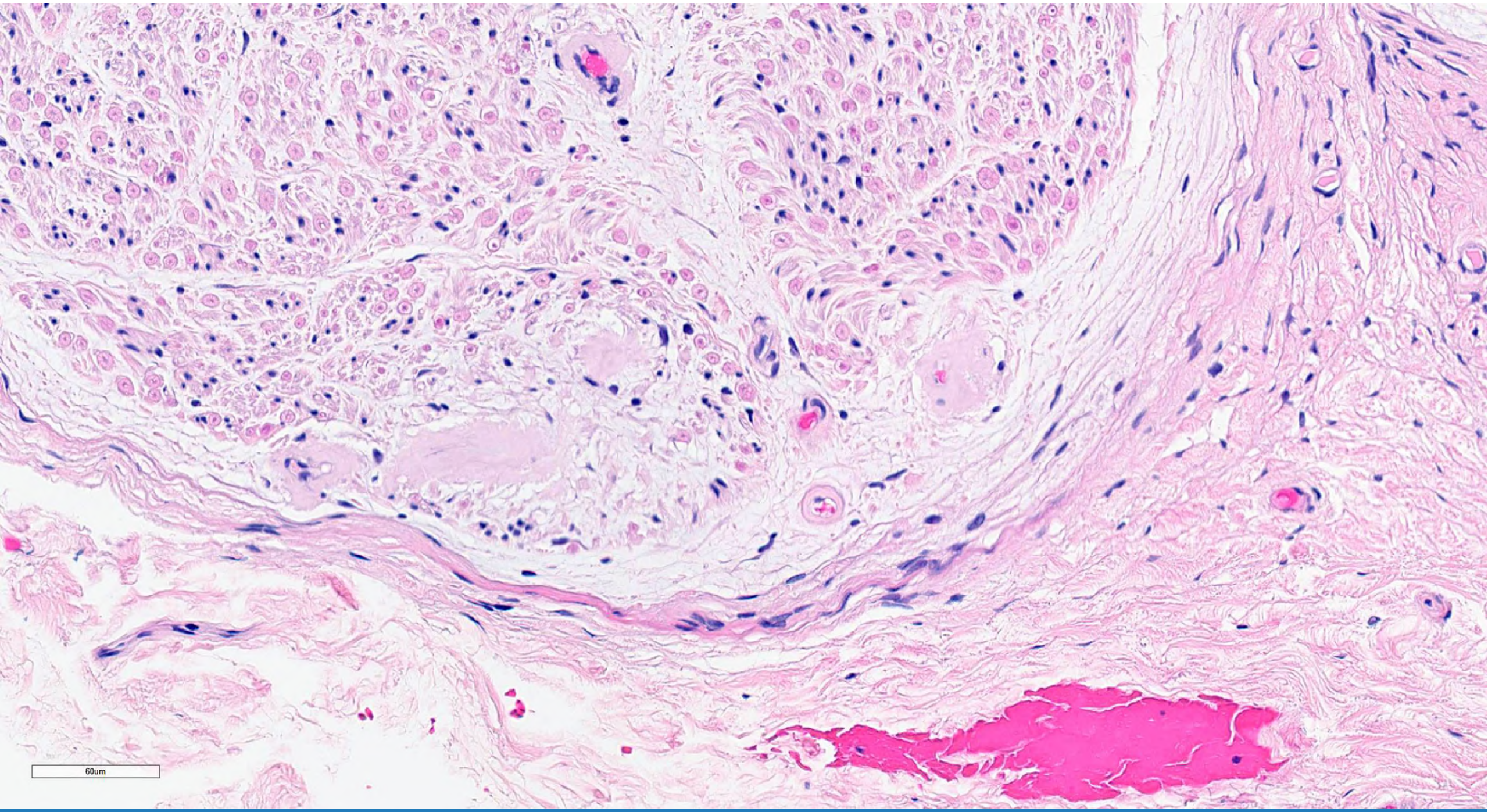
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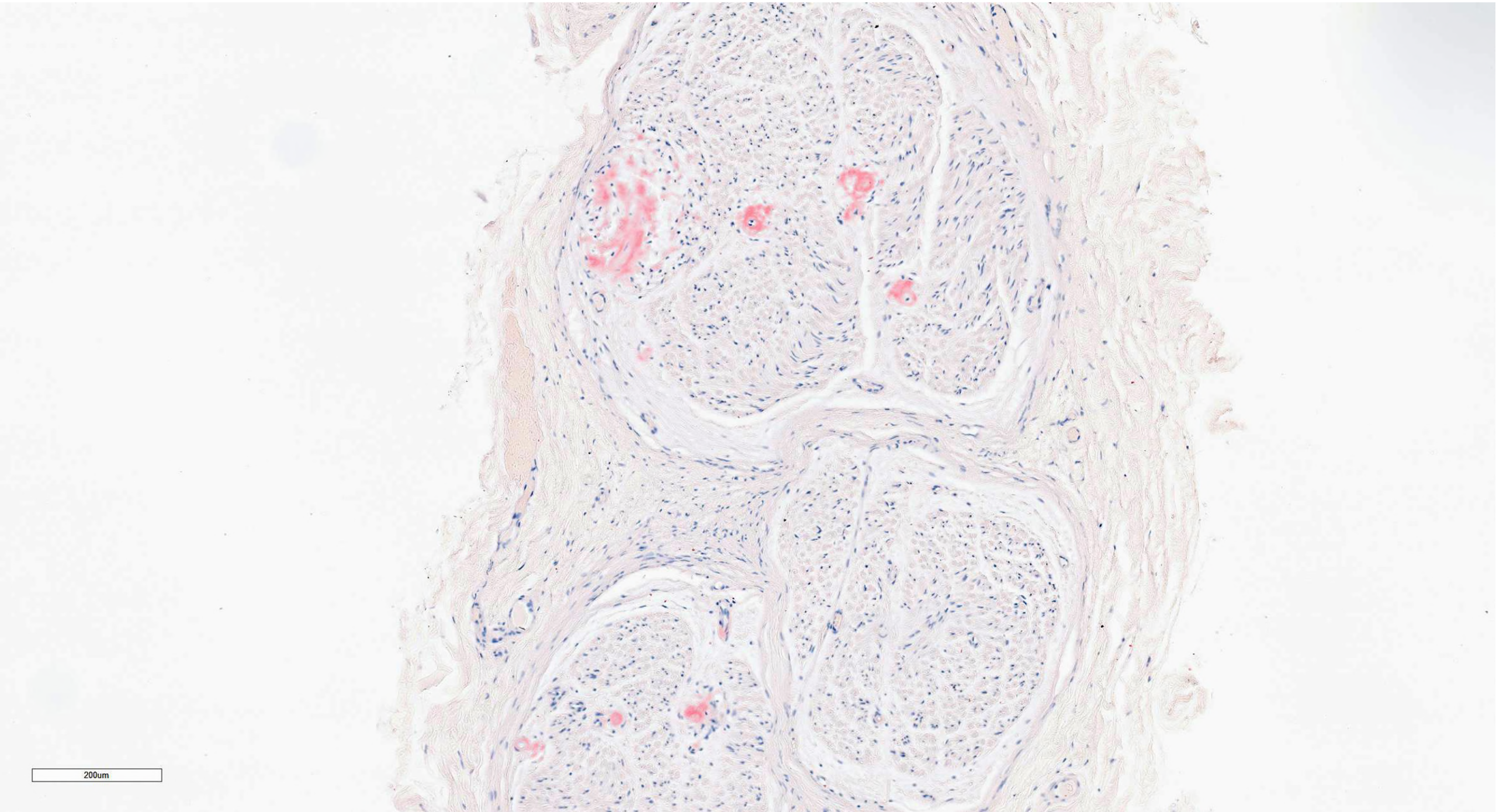
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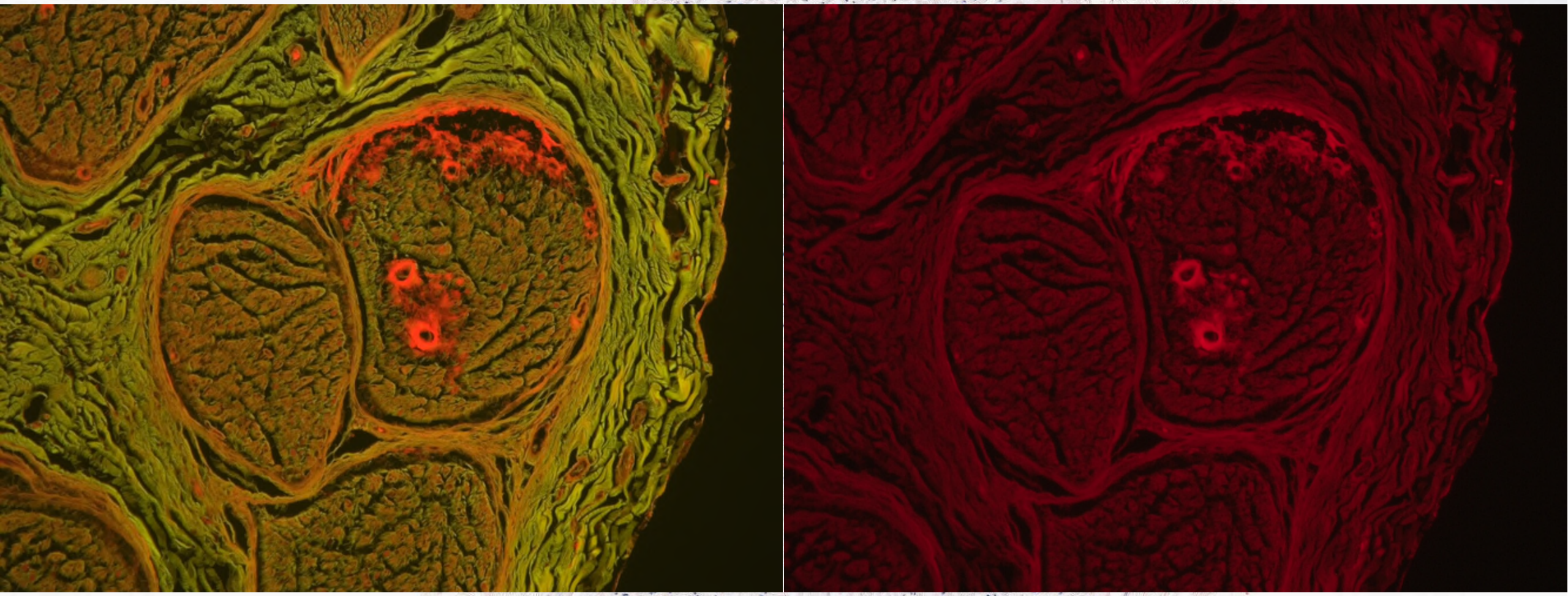
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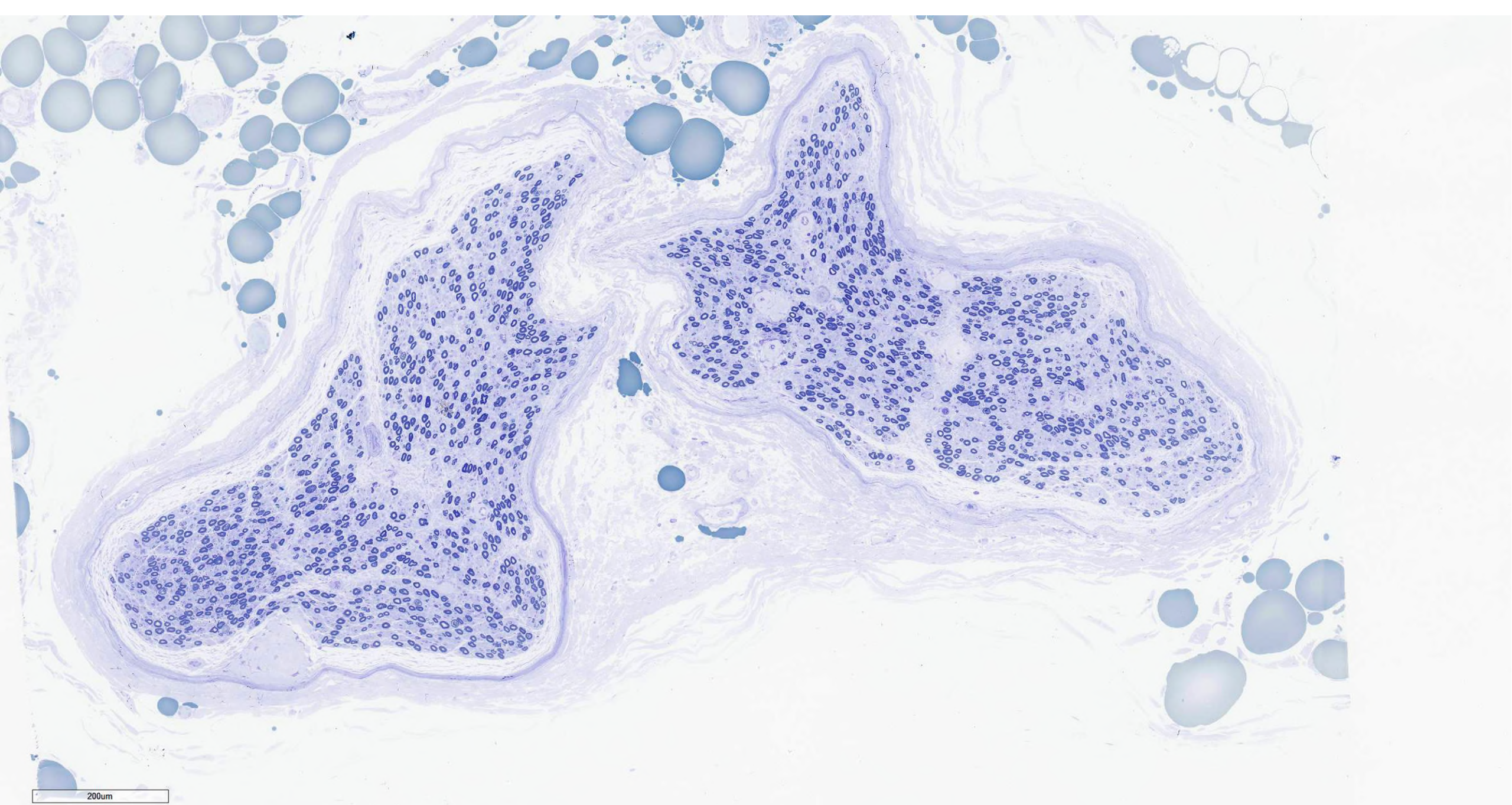
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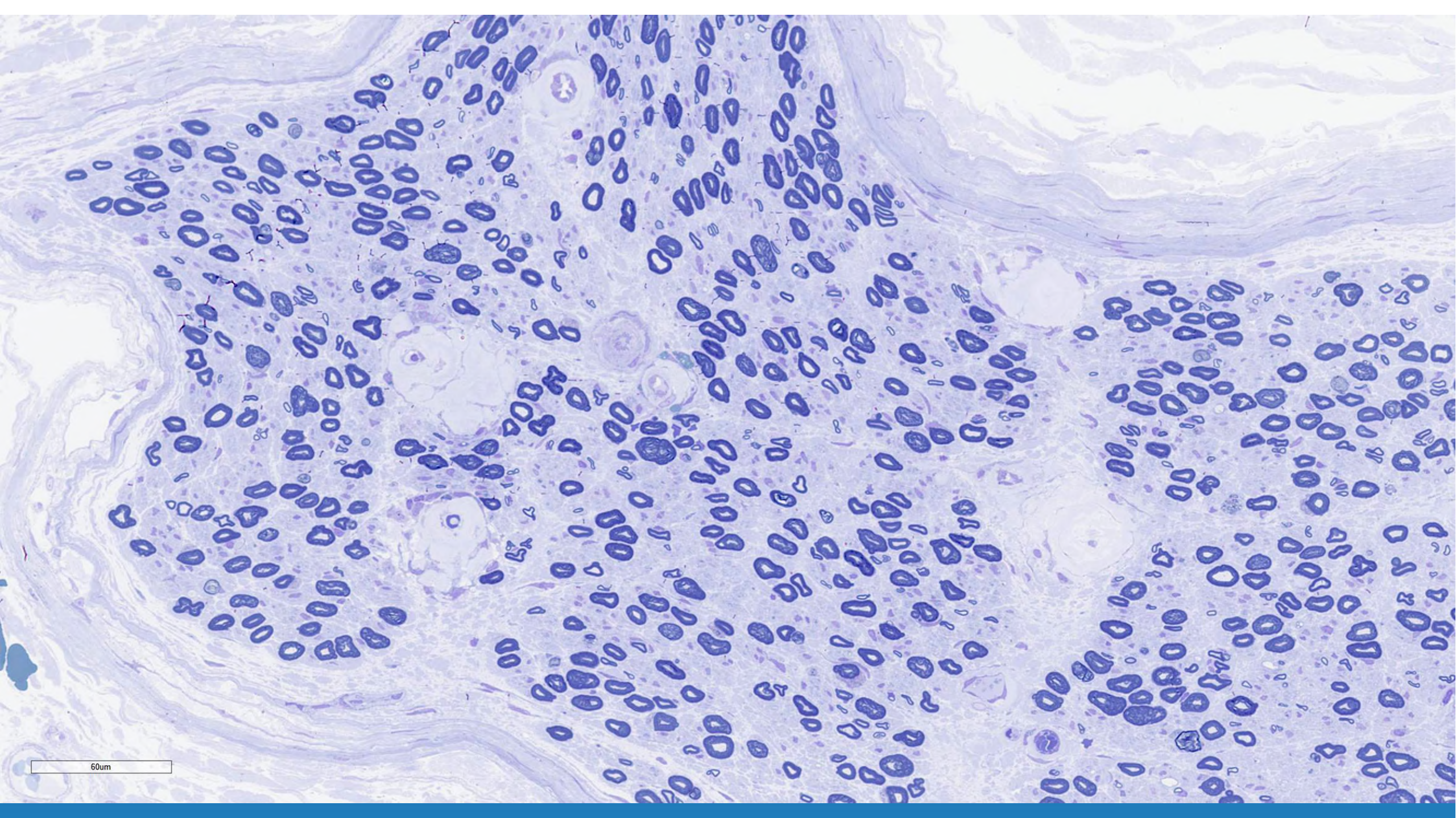
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Case 4

Diagnosis:

- Peripheral nerve with amyloid deposition and axonal loss

=> Subsequently found to have monoclonal IgA lambda

Amyloid Neuropathy

- Mainly light chain (AL) or transthyretin (ATTR) amyloid
- Phenotypic heterogeneity => frequent misdiagnosis
- Amyloid deposits can be focal => consider serial sections
- Epineurial or endoneurial connective tissue as well as vascular
- Mass spectrometry can aid in determining the type if clinical testing is inconclusive

PMID: 33629393 ; PMID: 33114611

Some pearls

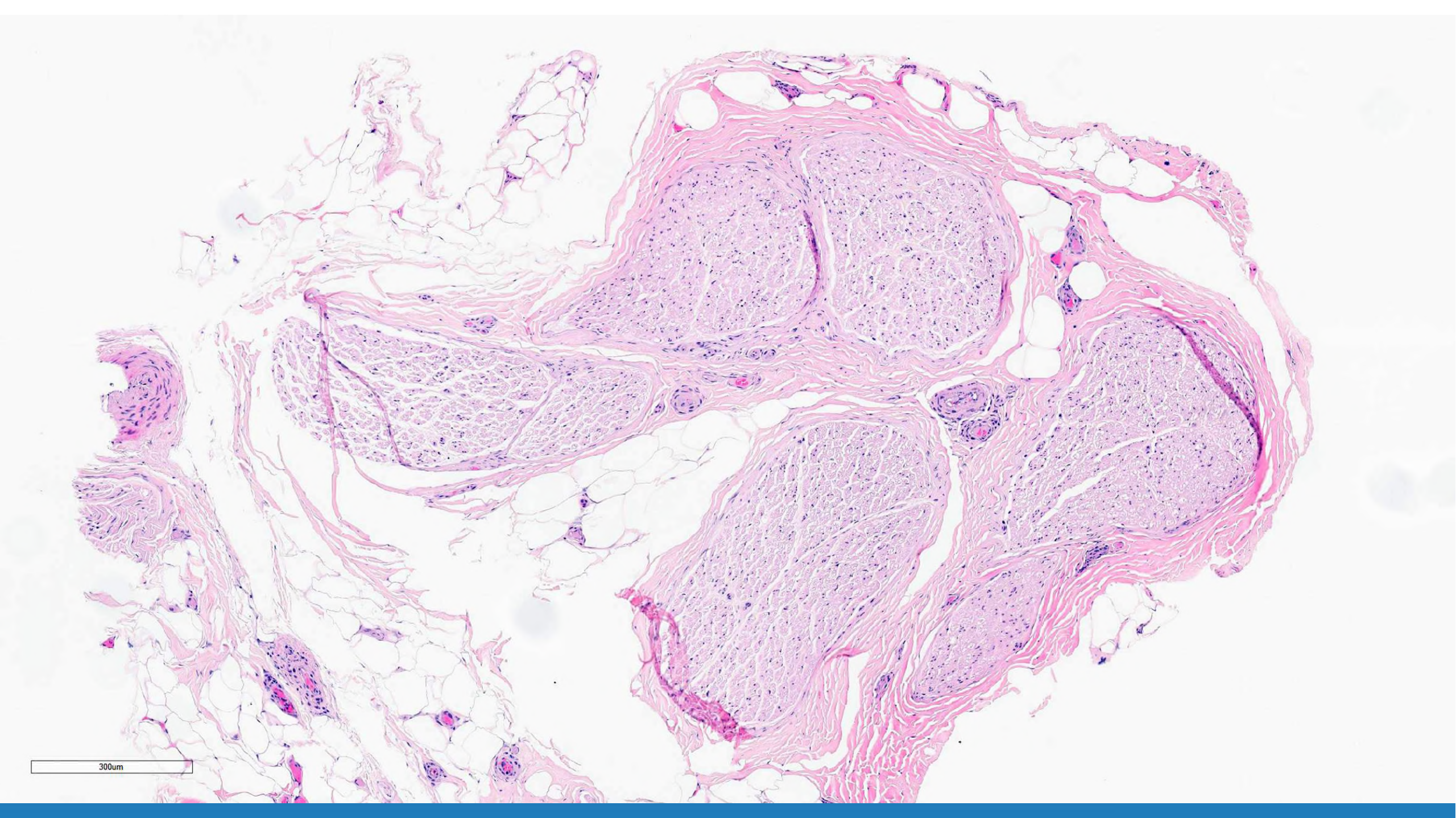
- Consider doing a Congo red stain on every biopsy

- Consider examining the Congo red stain on the IF scope

Case 5

Clinical history:

- 55-year-old who presented with subacute ascending weakness and some numbness that evolved over 2 weeks
- Had some flu-like symptoms
- Initially treated as AIDP / GBS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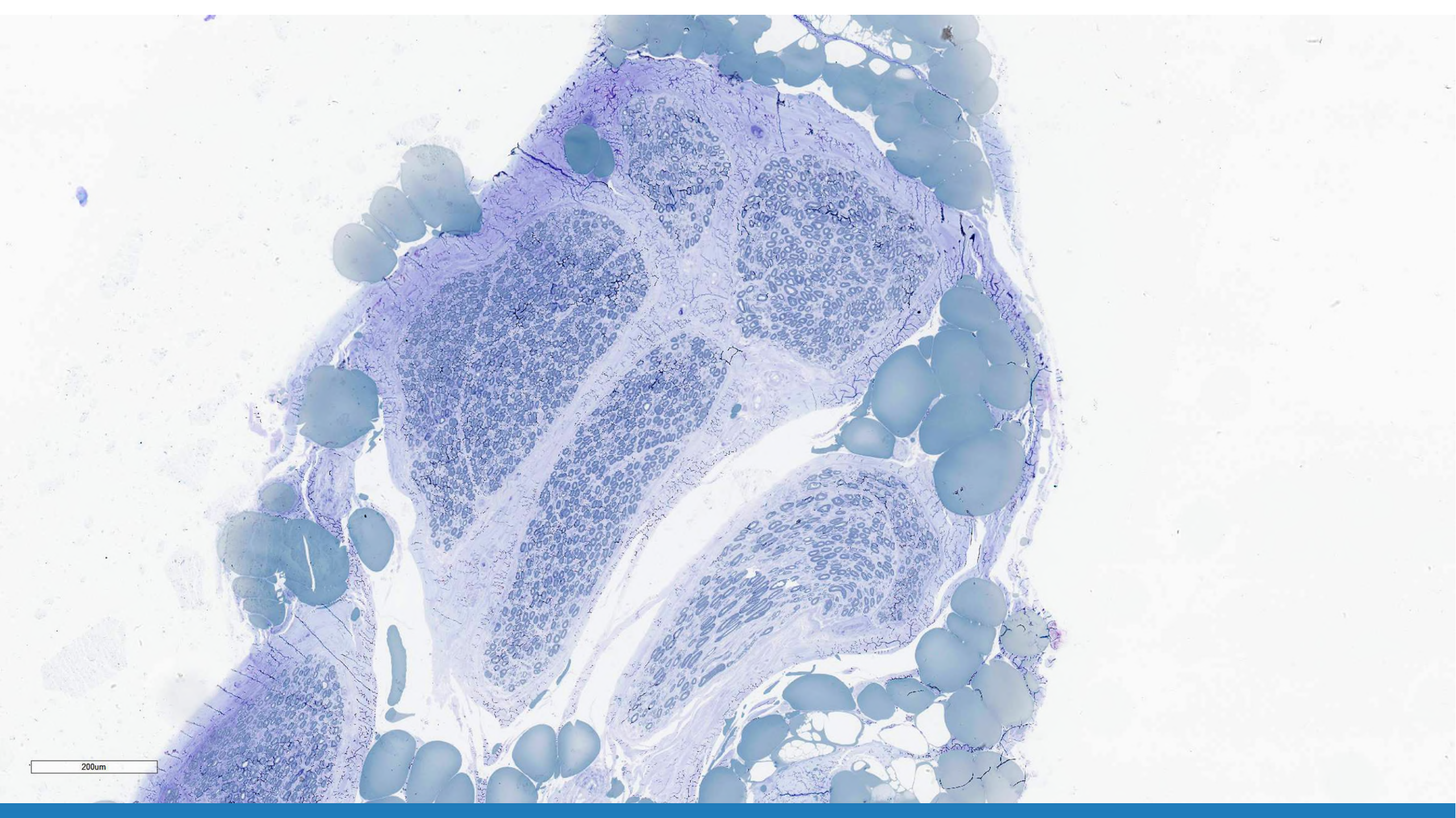
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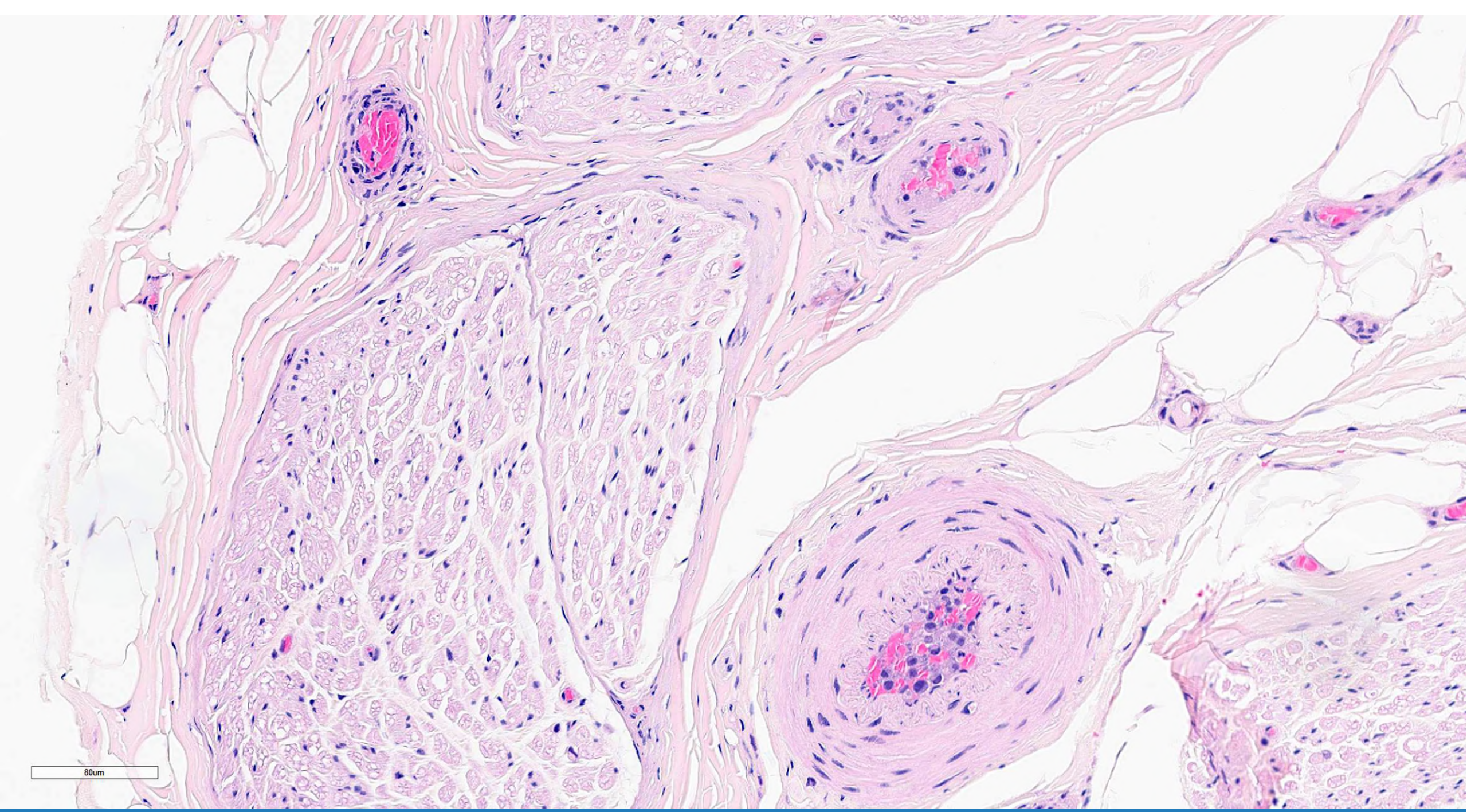
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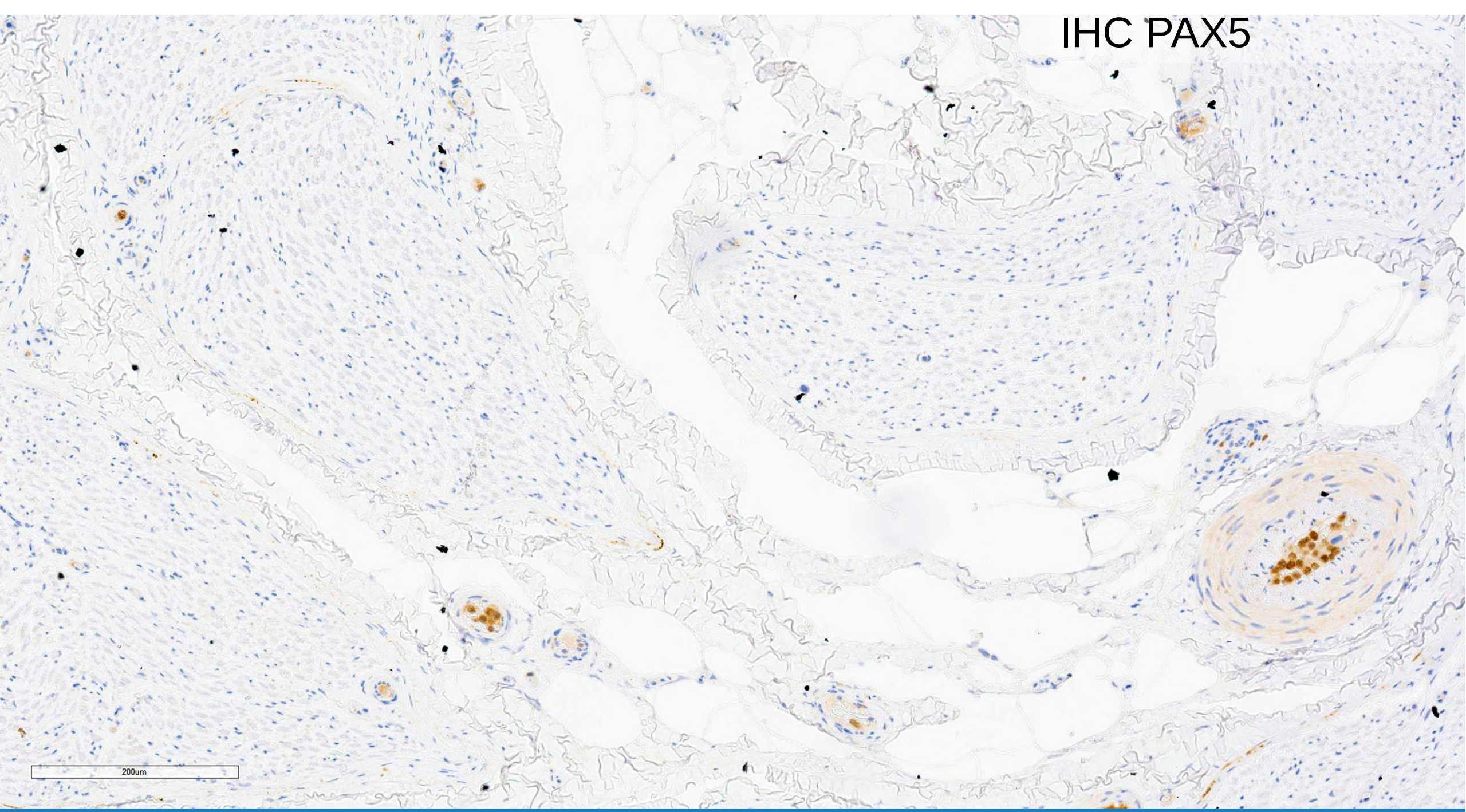
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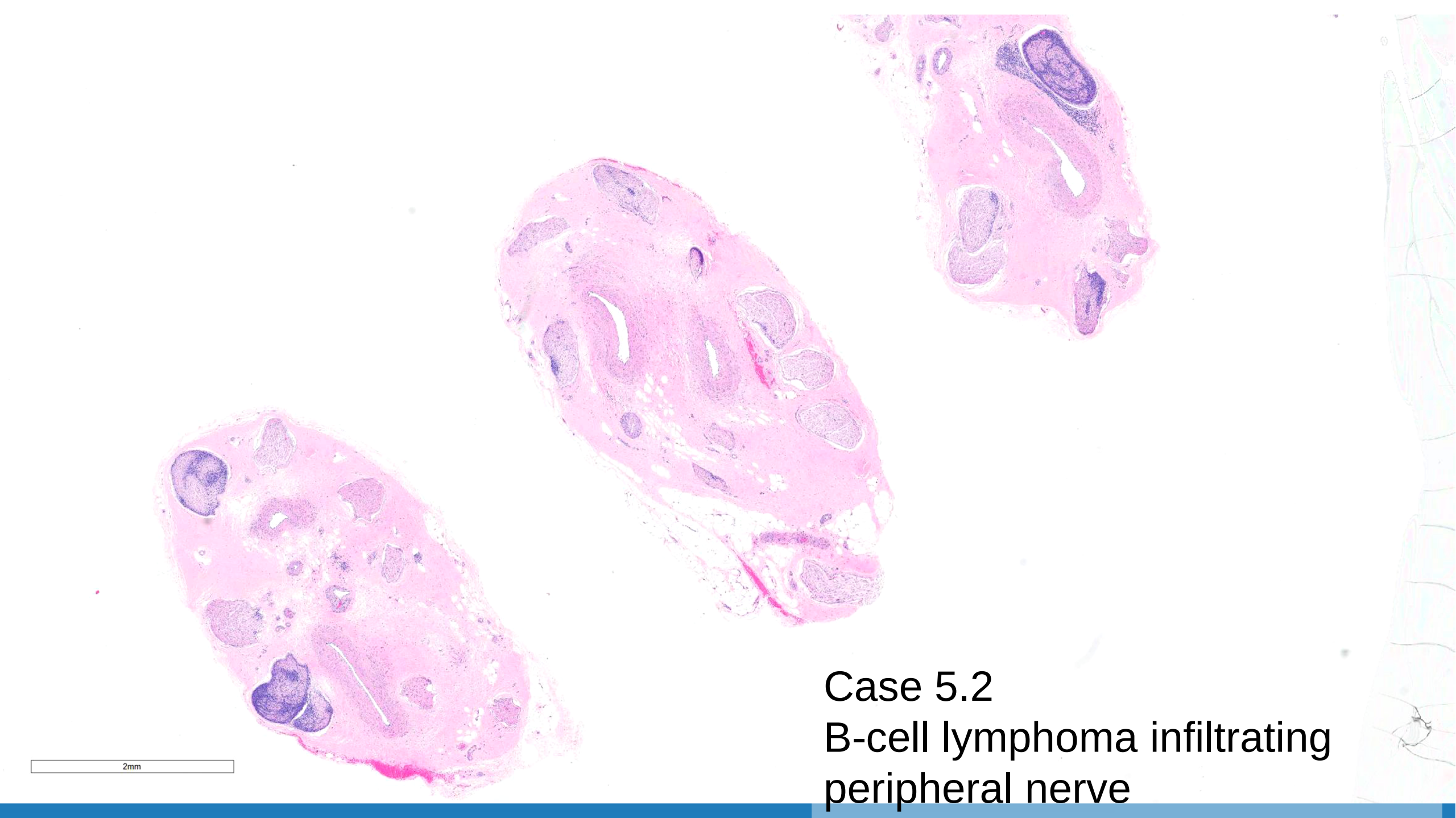
Case 5

Diagnosis:

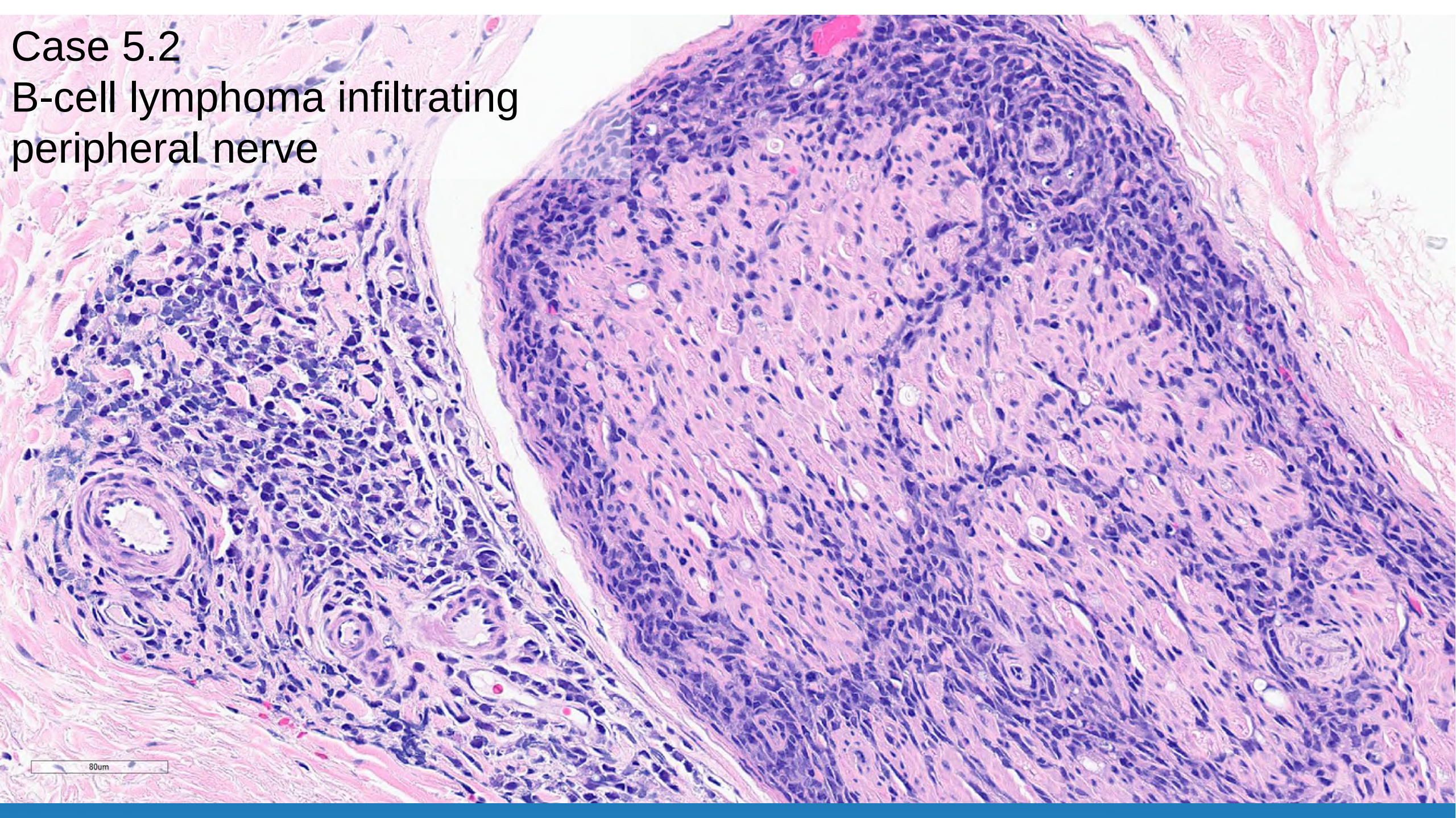
Intravascular large B-cell lymphoma

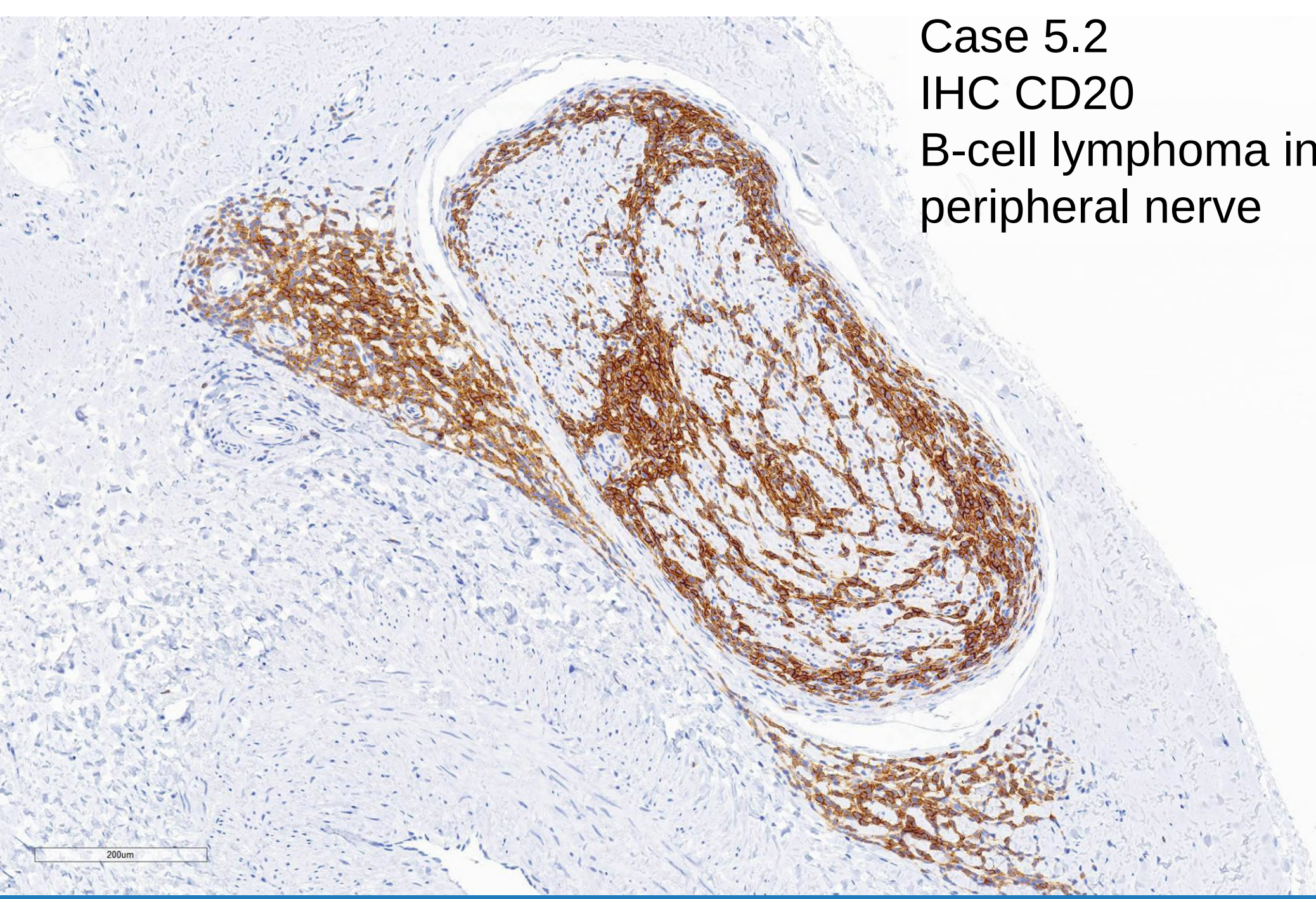
=> Patient passed within weeks and an autopsy showed involvement of brain, lungs, heart, as well as other organs.



Case 5.2
B-cell lymphoma infiltrating peripheral nerve

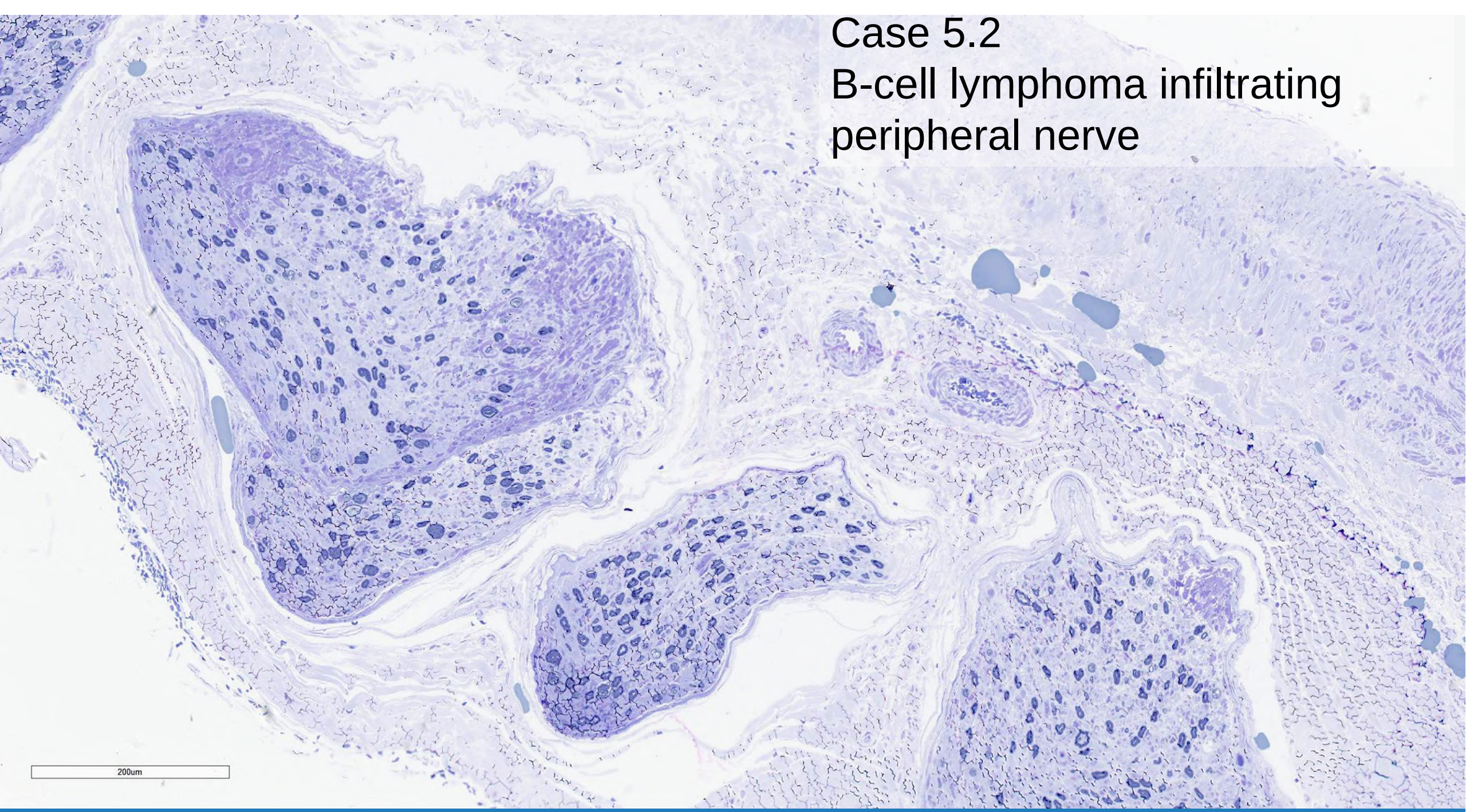
Case 5.2
B-cell lymphoma infiltrating peripheral nerve





Case 5.2
IHC CD20
B-cell lymphoma infiltrating peripheral nerve

Case 5.2
B-cell lymphoma infiltrating peripheral nerve



Neurolymphomatosis / Lymphoma in Nerves

- Neoplastic infiltration of peripheral nerves, usually non-Hodgkin lymphoma
- Presentation heterogeneous
- Can be the initial presentation
- Clonality studies help with the distinction from inflammatory conditions

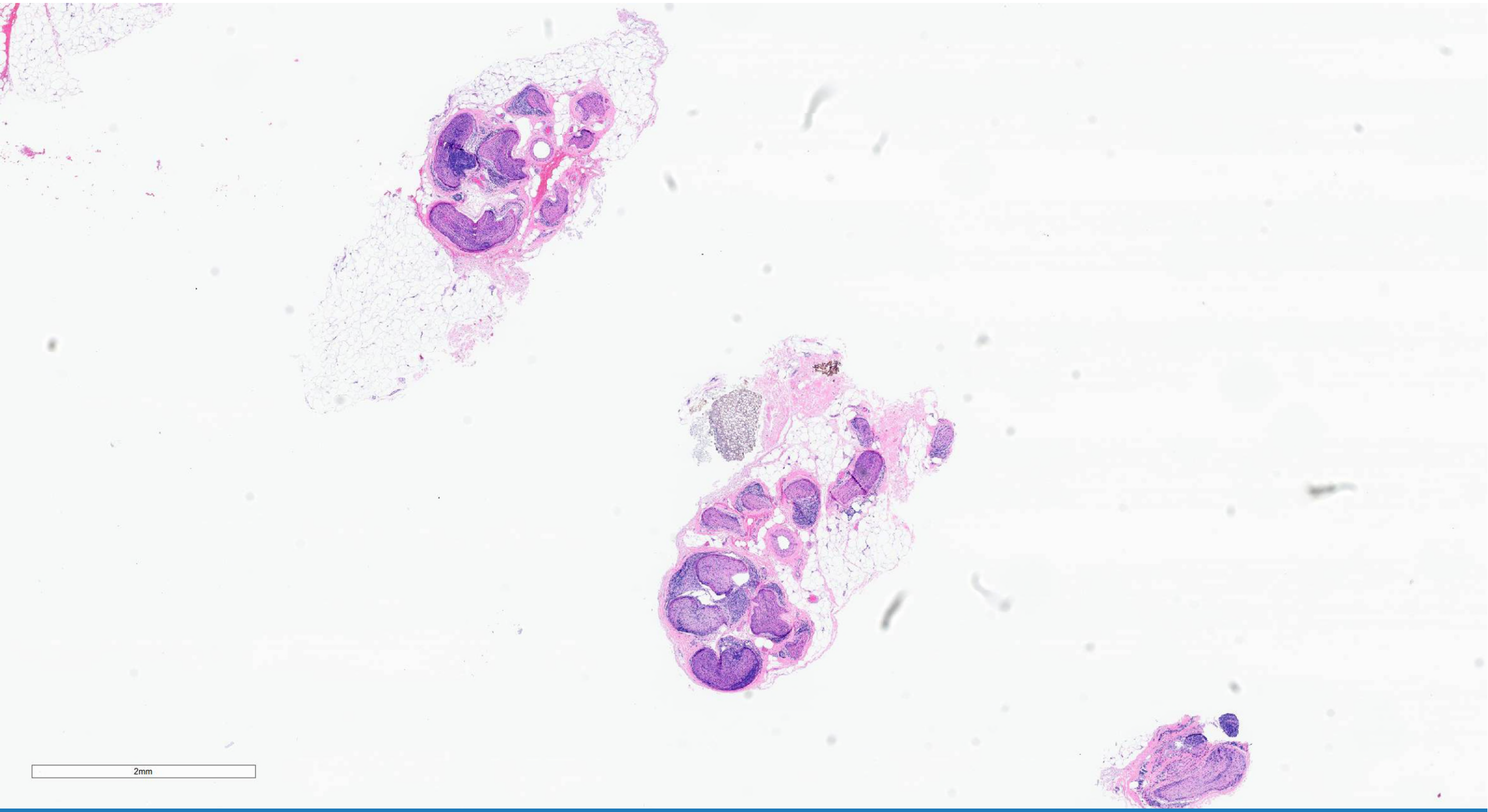
Some pearls

- Don’t forget to look at other details beyond axons on the Epon sections (cellular infiltrates, vascular changes, …)

Case 6

Clinical history:

- 44-year-old who started to have paresthesia in the lateral foot.
- Symptoms spread to involve the left side.
- Symptoms deteriorating.
- An EMG shows features with an axonal (sensory > motor) polyneuropathy.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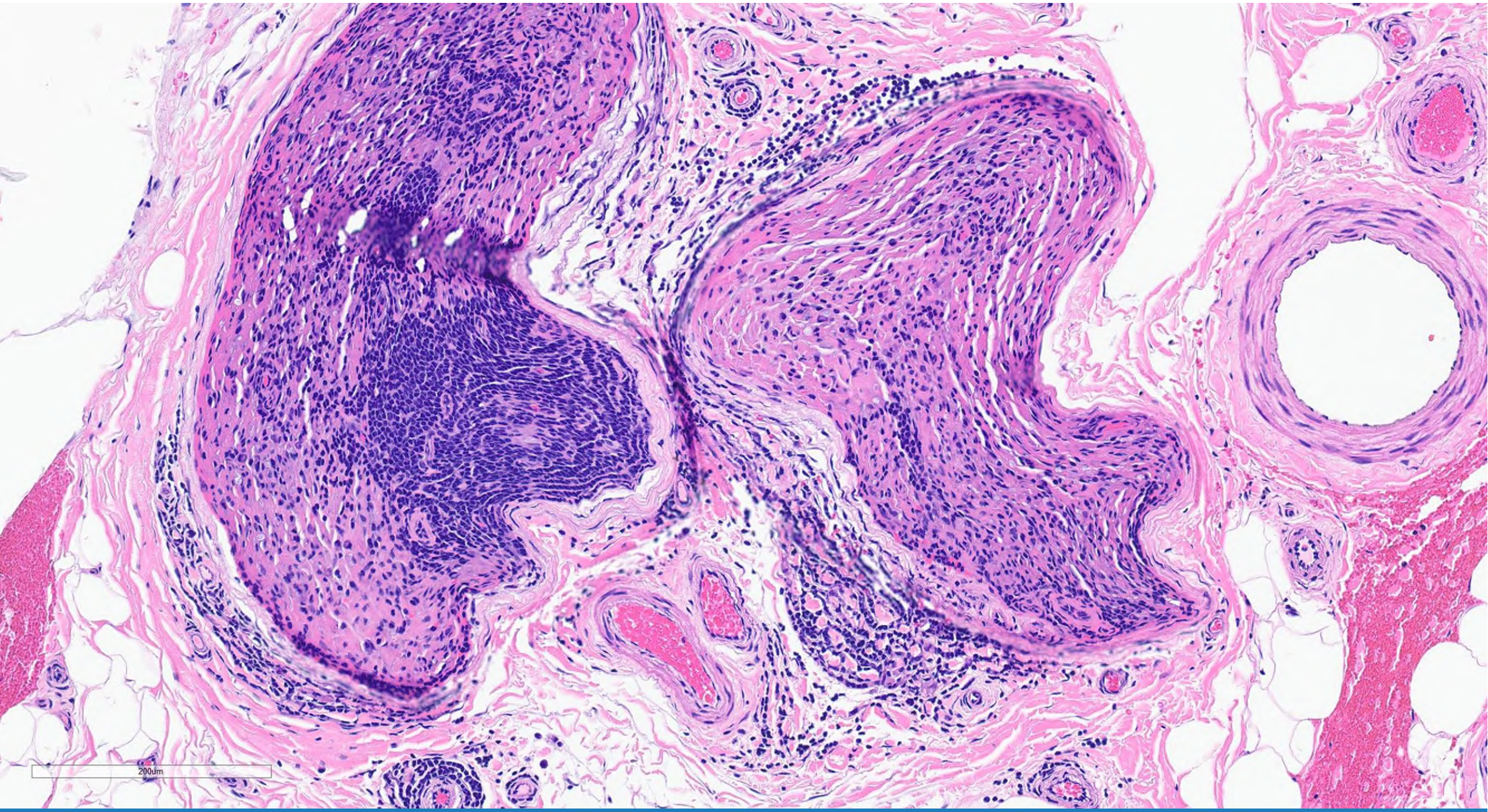
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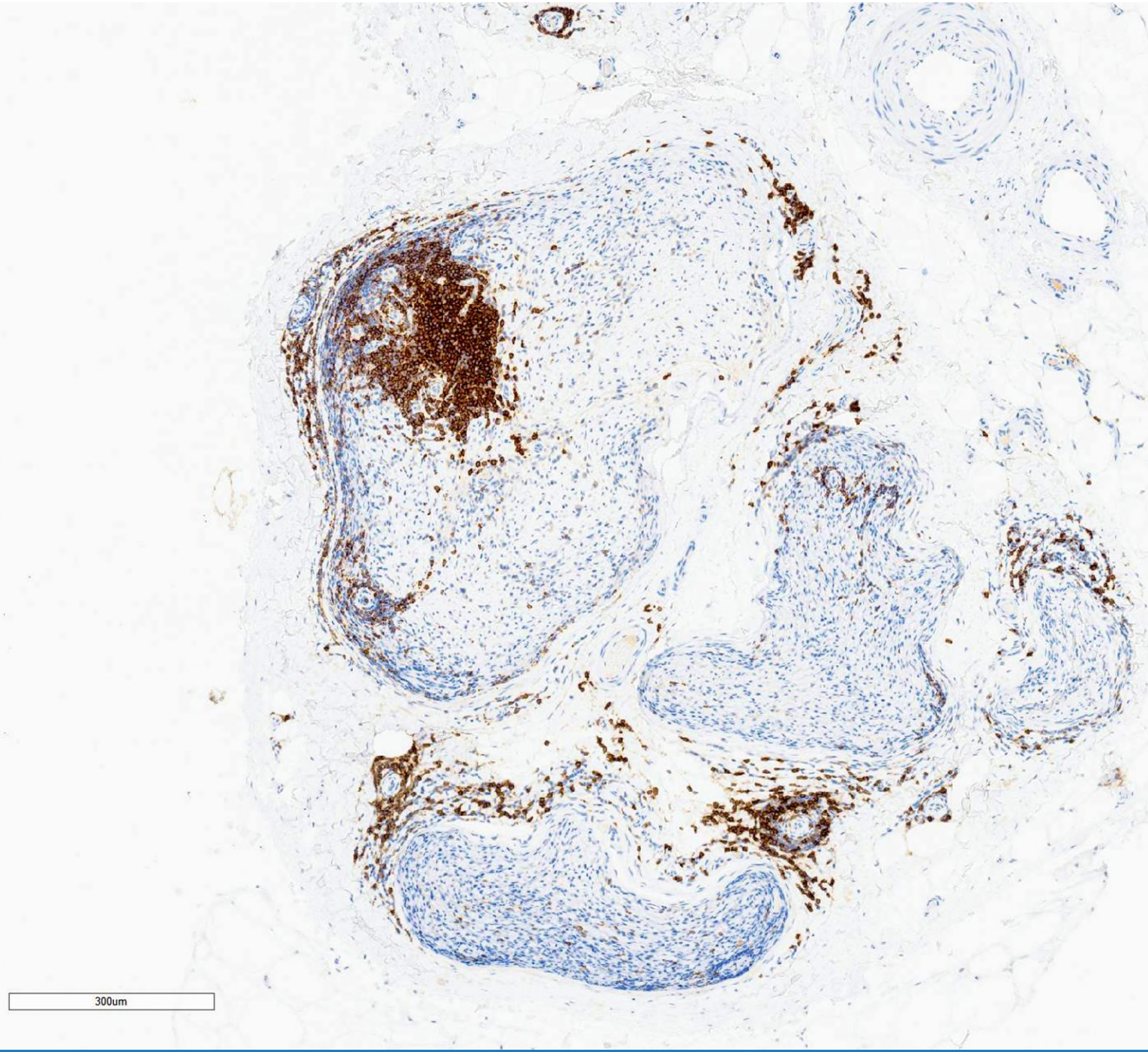

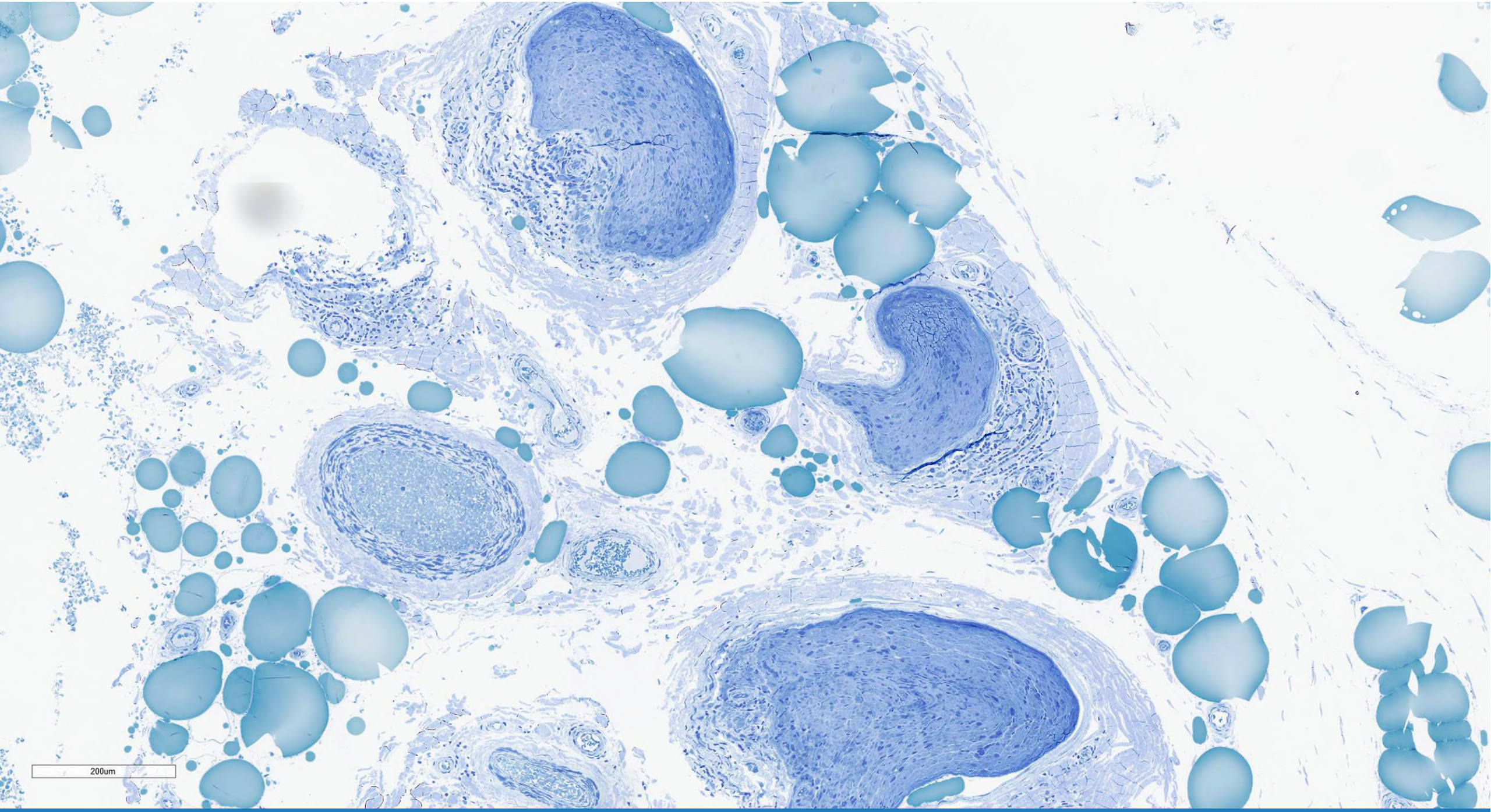
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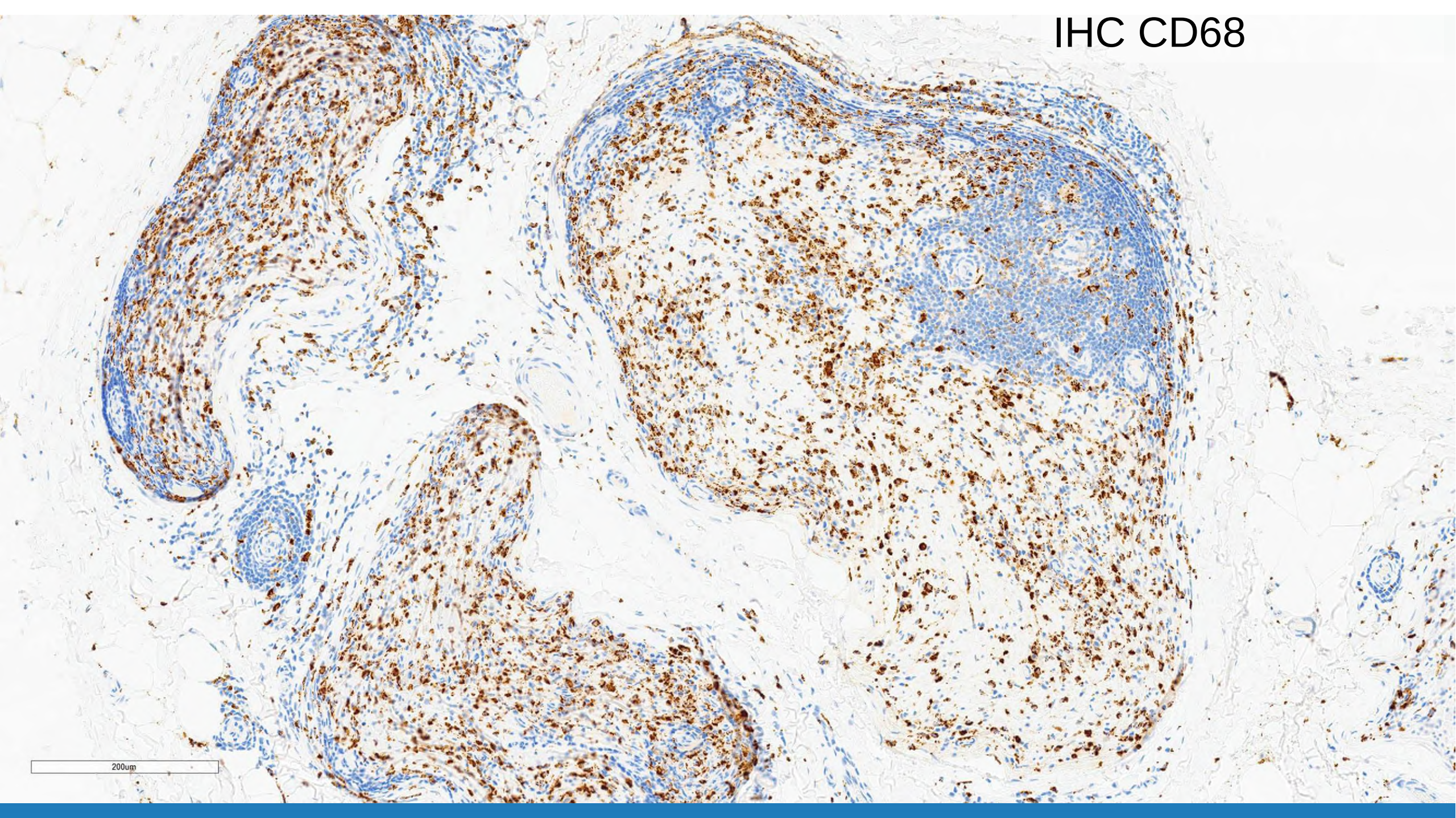
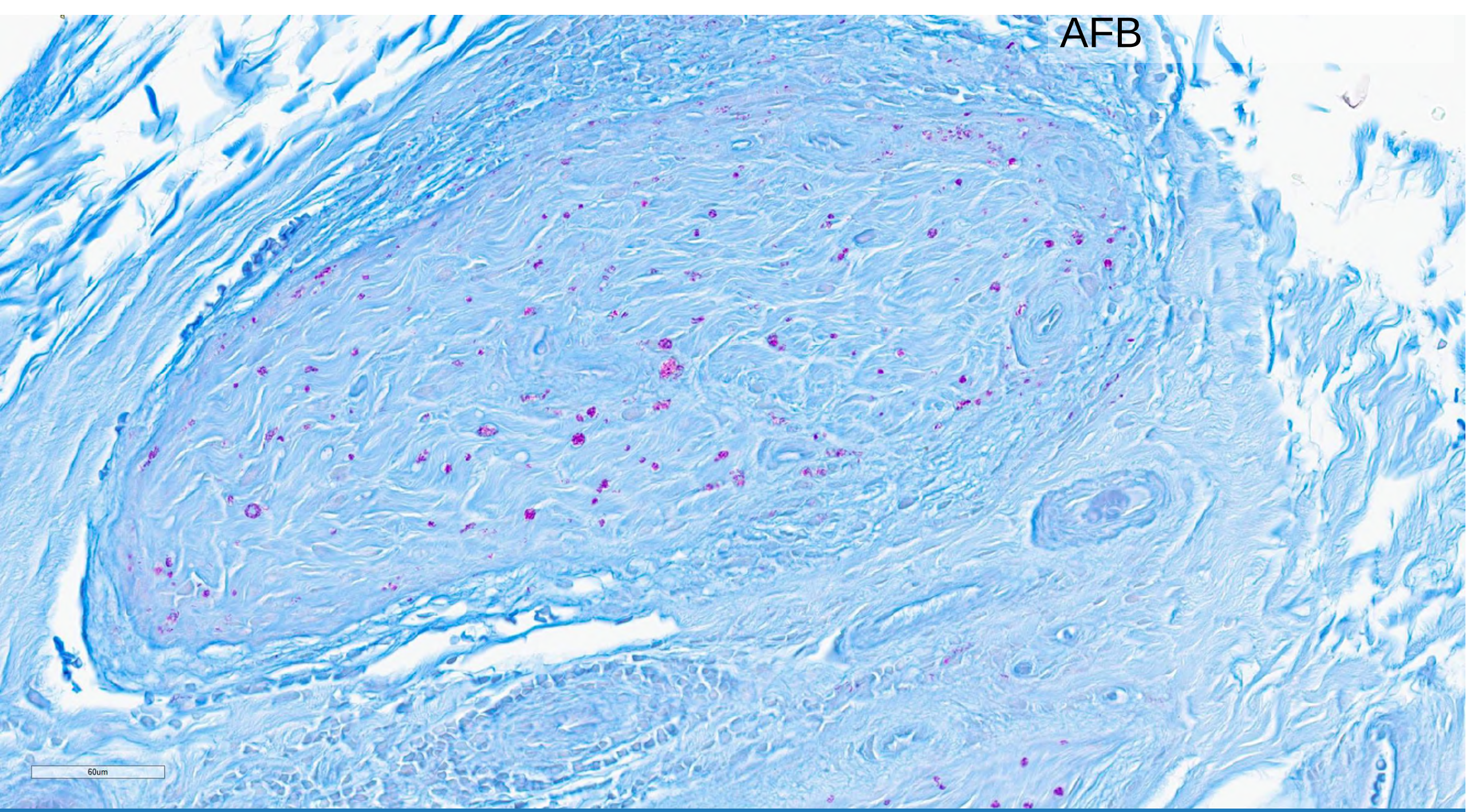
Case 6

Diagnosis:

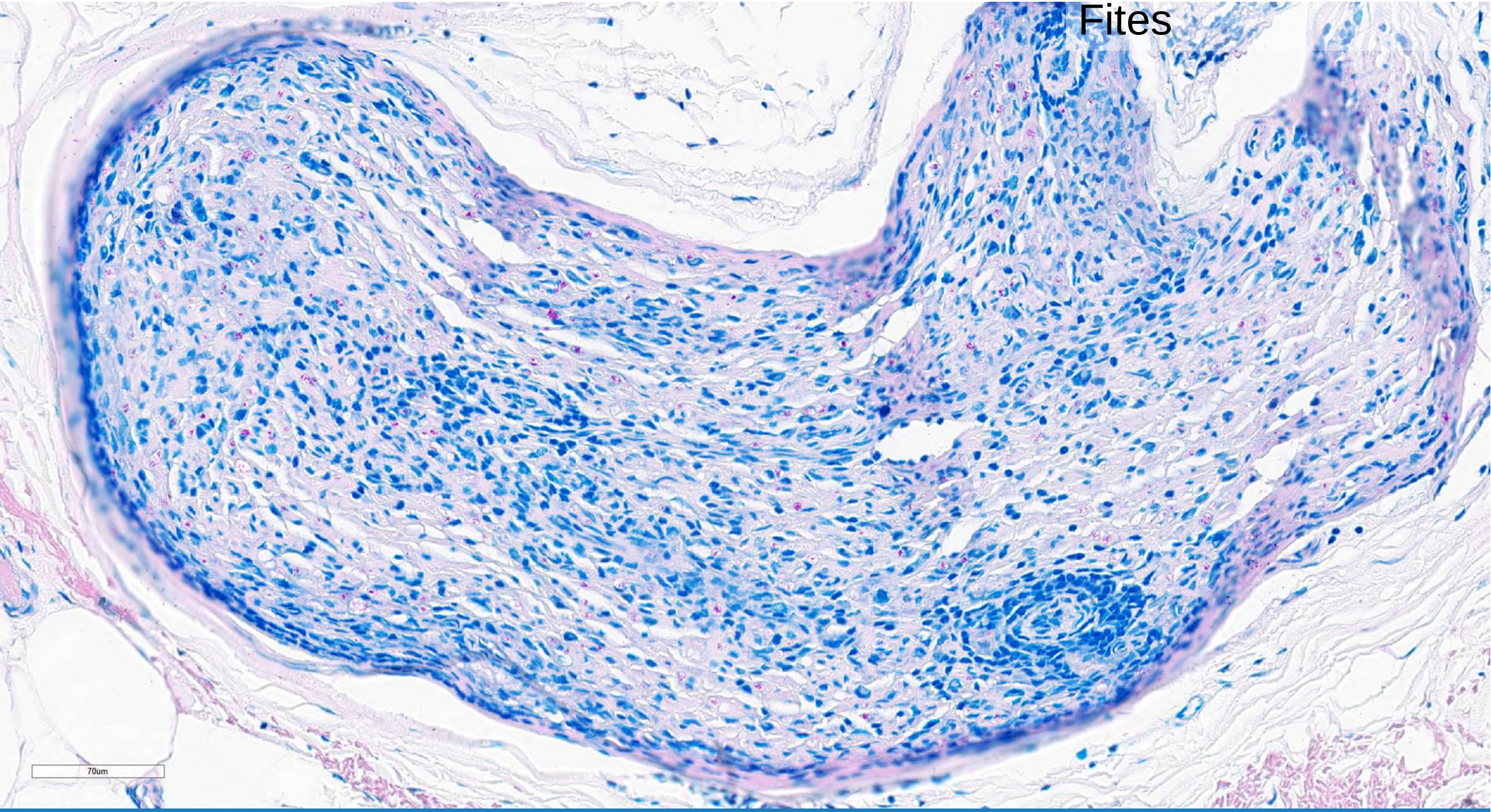
Initial diagnosis: worrisome for involvement by B-cell lymphoma

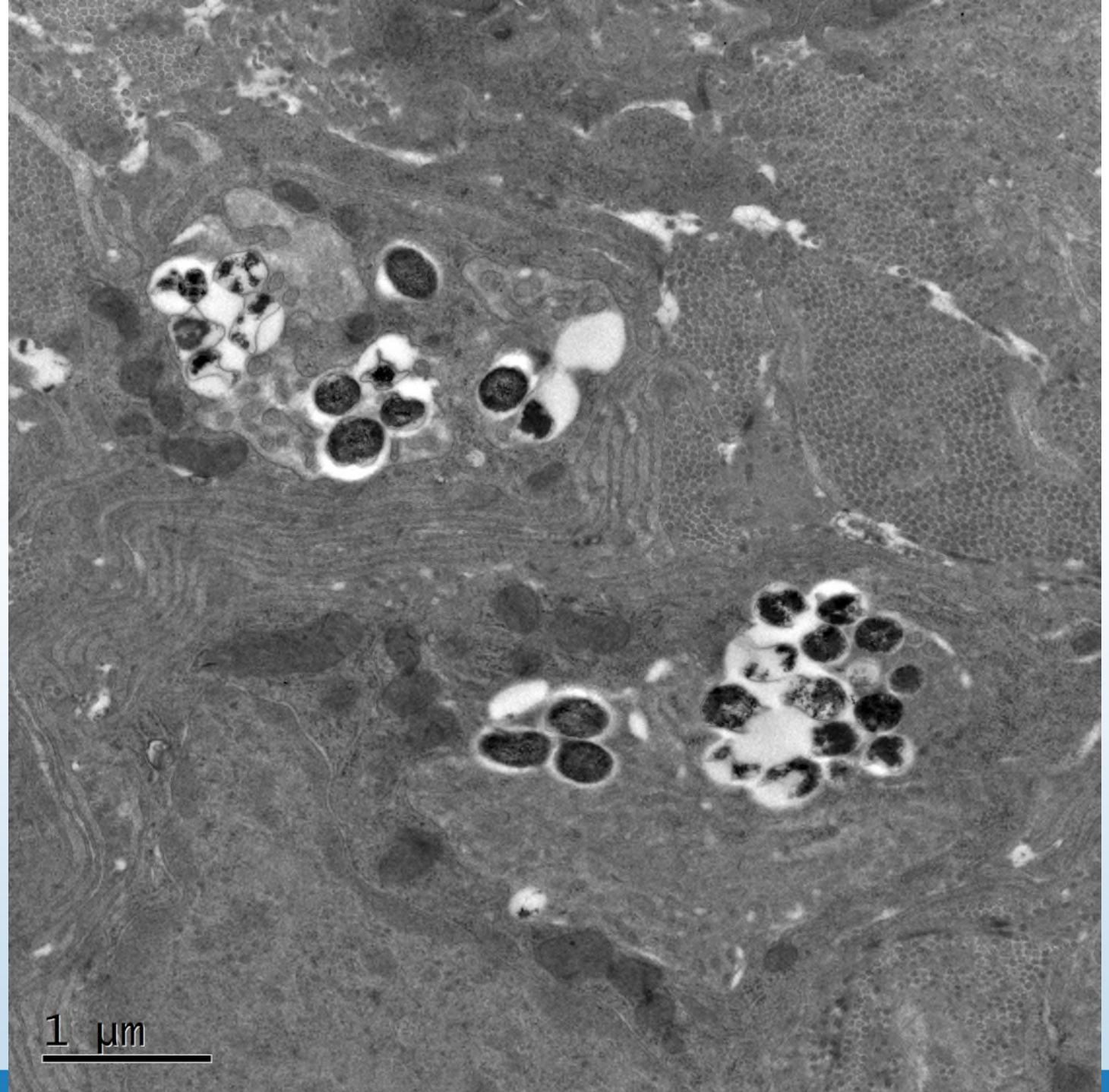
=> Molecular studies negative; in the meantime the pathology was reviewed elsewhere.


IHC CD68
200um


AFB
60um

Fites




1 µm

Case 6

Diagnosis:

Lepromatous leprosy (AFB / Fites positive; confirmed by PCR based testing)

=> Clinically purely neuritic leprosy.

=> No granulomas; histology may mimic nerve involvement by lymphoma

Infections / Leprosy

- Pure neuritic leprosy accounts for 4% to 8% of cases
- Acid fast bacilli within foam cells and Schwann cells
- Bacilli primarily in lepromatous leprosy
- Tuberculoid leprosy: granulomas but usually no bacilli
- PCR testing increases the sensitivity

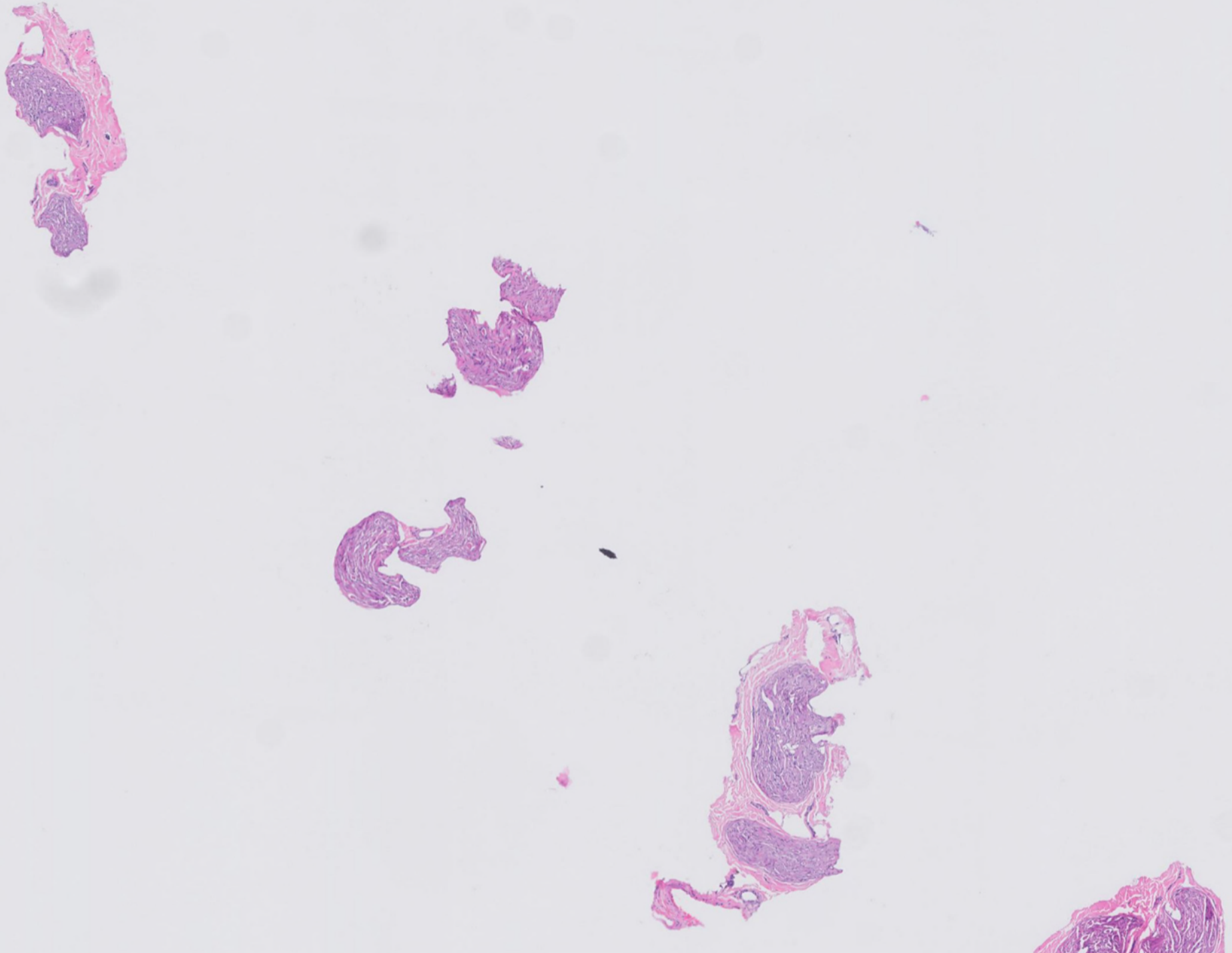
Some pearls

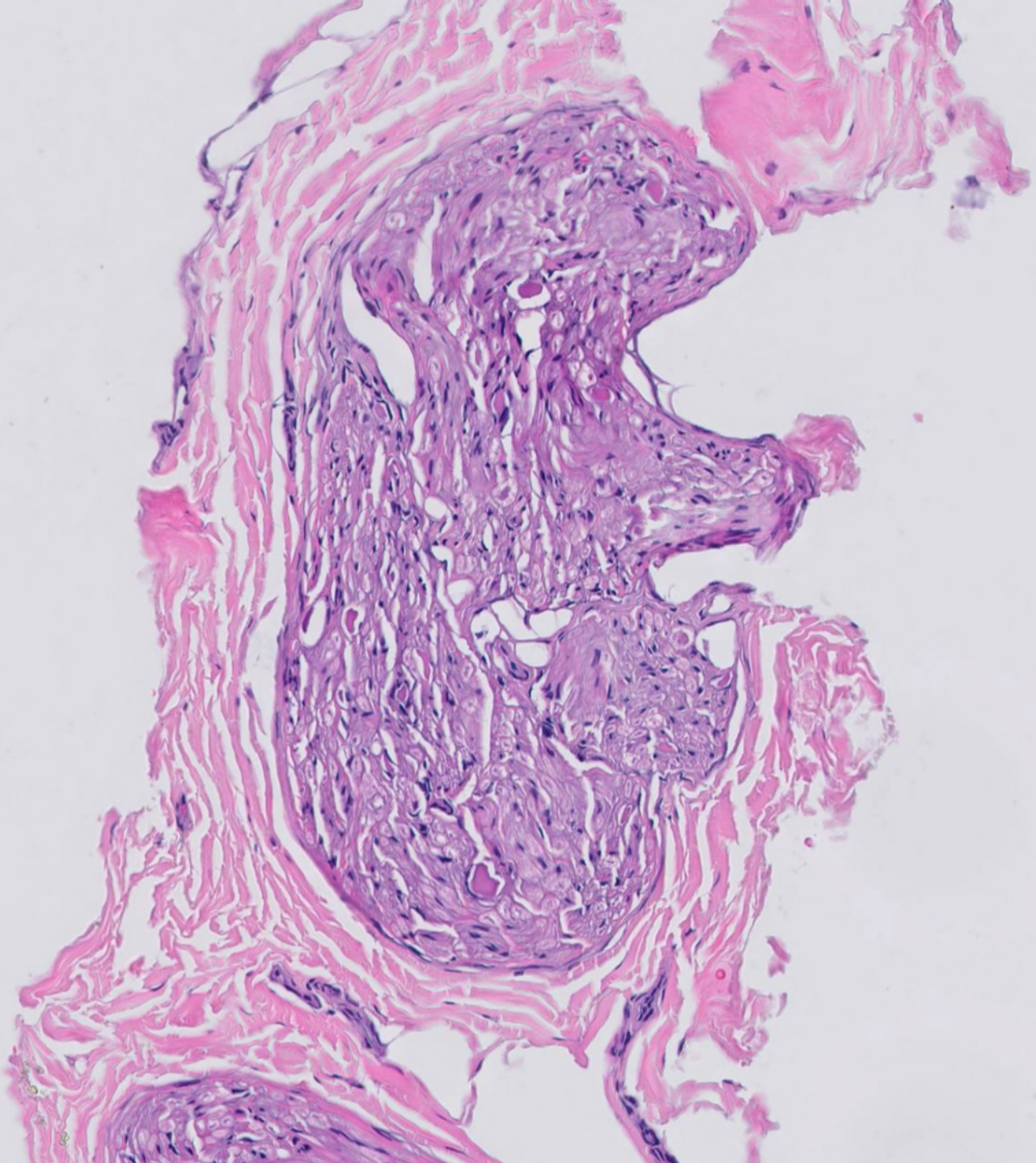
- Leprosy does not have to be associated with granulomas.

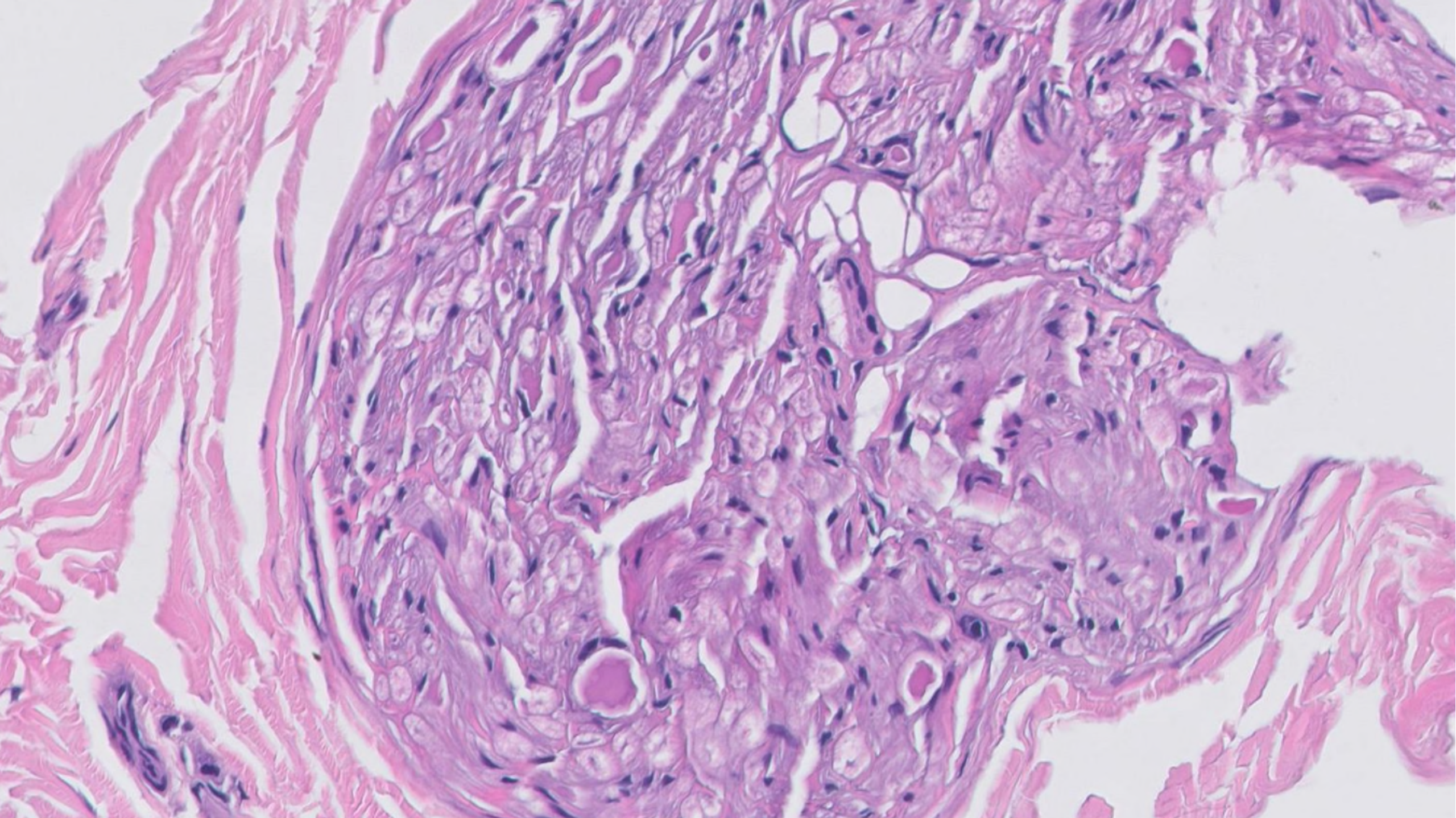
Case 7

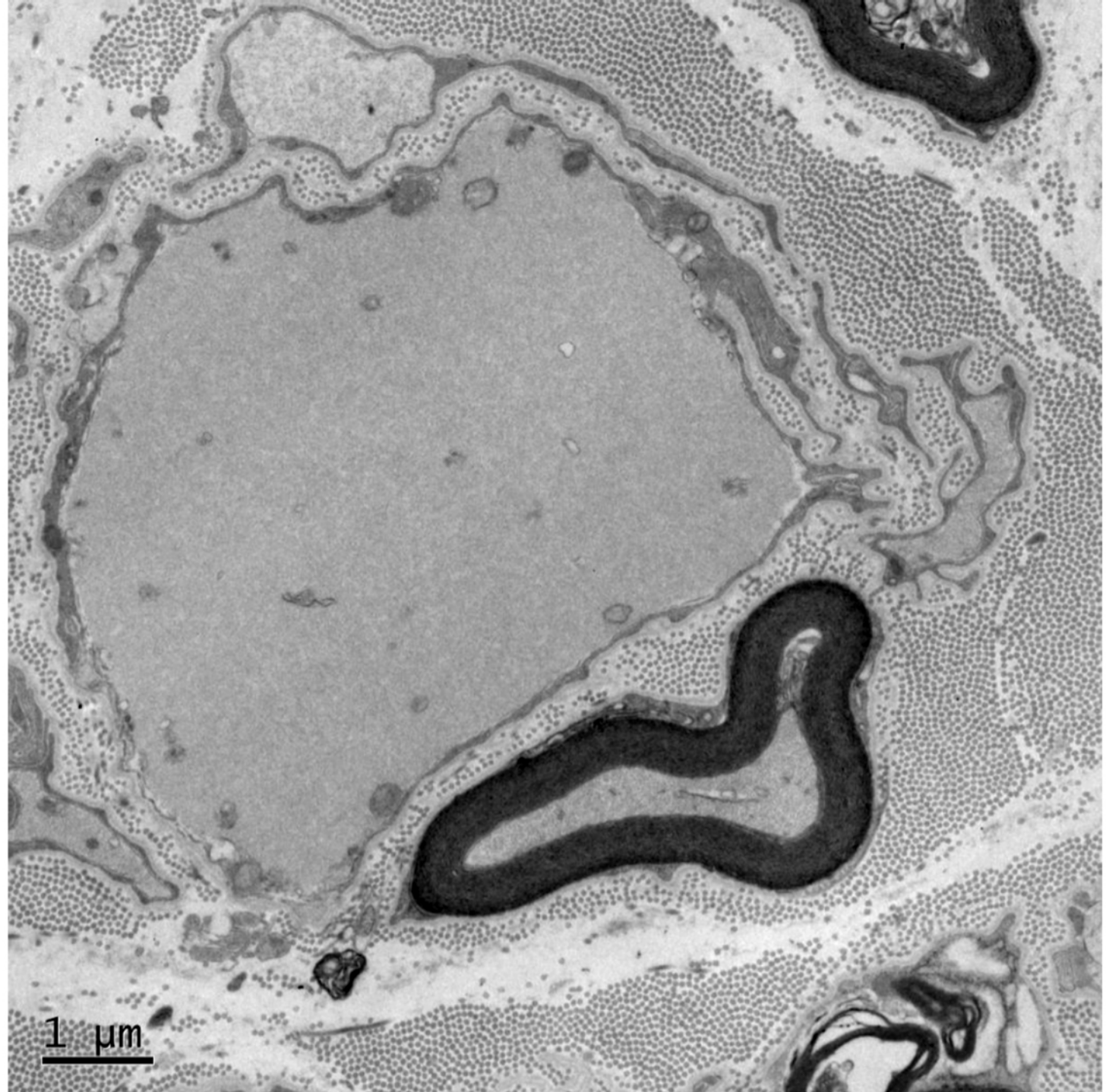
Clinical history:

- 9-year-old female born at term with unremarkable early motor development.
- Noted to be clumsy by her parents.
- At age 6 she had generalized hypotonia, prominent bilateral pes cavus and hammertoes, weakness in dorsiflexion of the feet and inversion of the feet. Sensation for vibration seemed decreased.
- EMG showed features of an axonal neuropathy.





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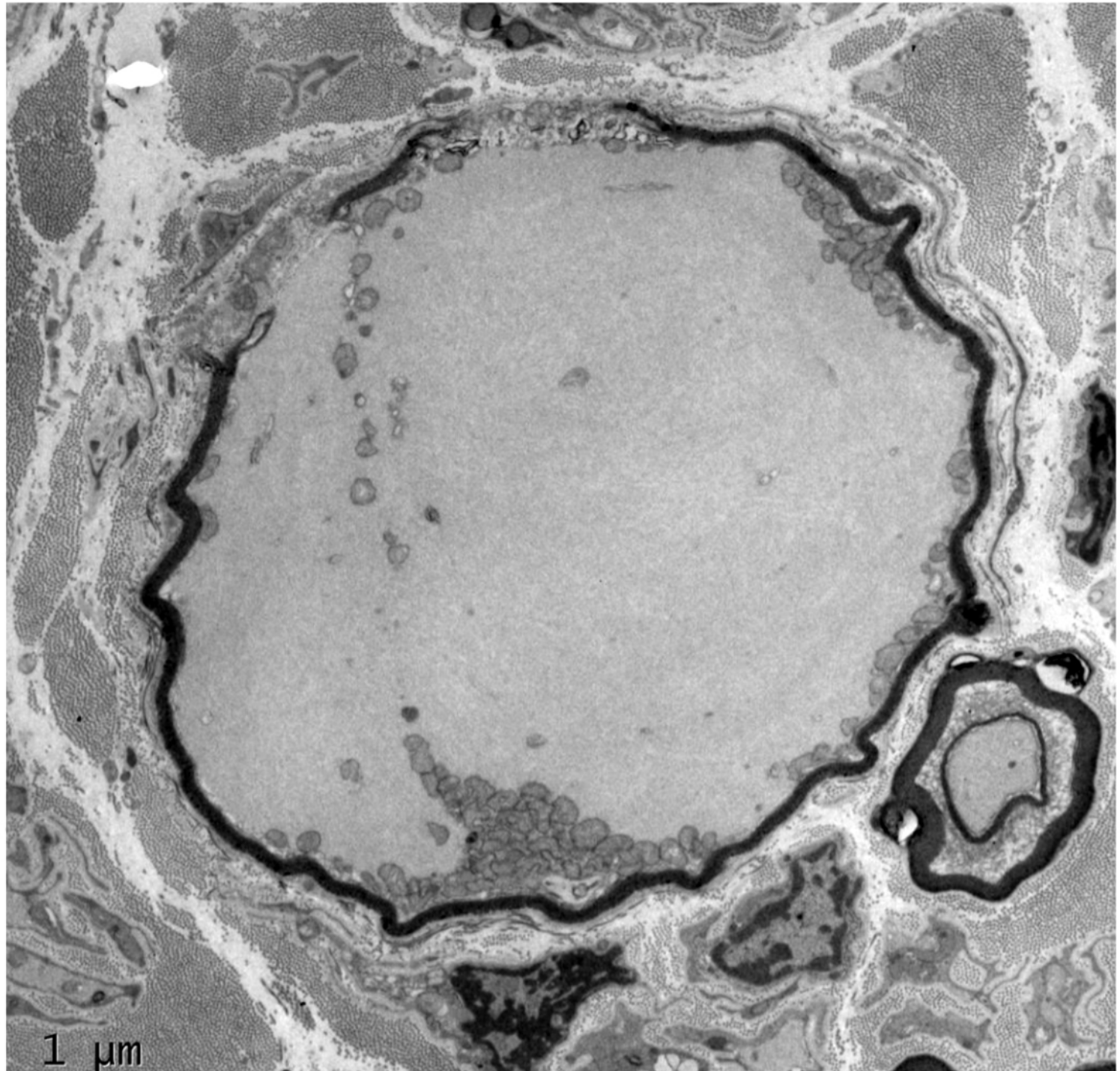

1 µm

Case 7

Diagnosis:

Giant axonal neuropathy

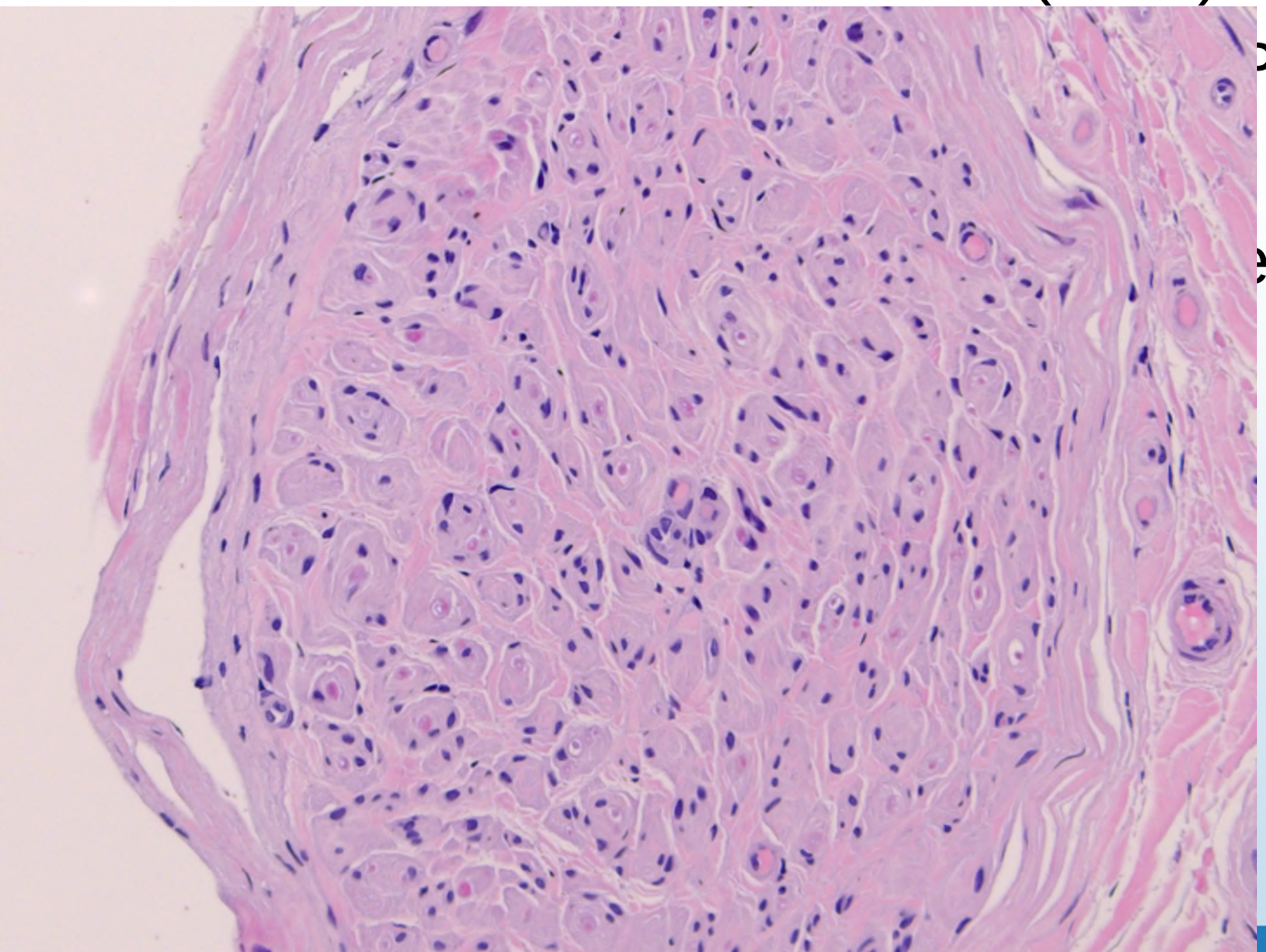
=> Clinically documented to have *GAN* variants

Hereditary diseases / hereditary neuropathies

- Giant axonal neuropathy
- Charcot-Marie-Tooth (CMT)
- Hereditary Neuropathy with Pressure Palsies (HNPP)
- Storage diseases / Leukodystrophies
- Adult polyglucosan body disease

Hereditary diseases / hereditary neuropathies

- Giant axonal neuropathy
- Charcot-Marie-Tooth (CMT)

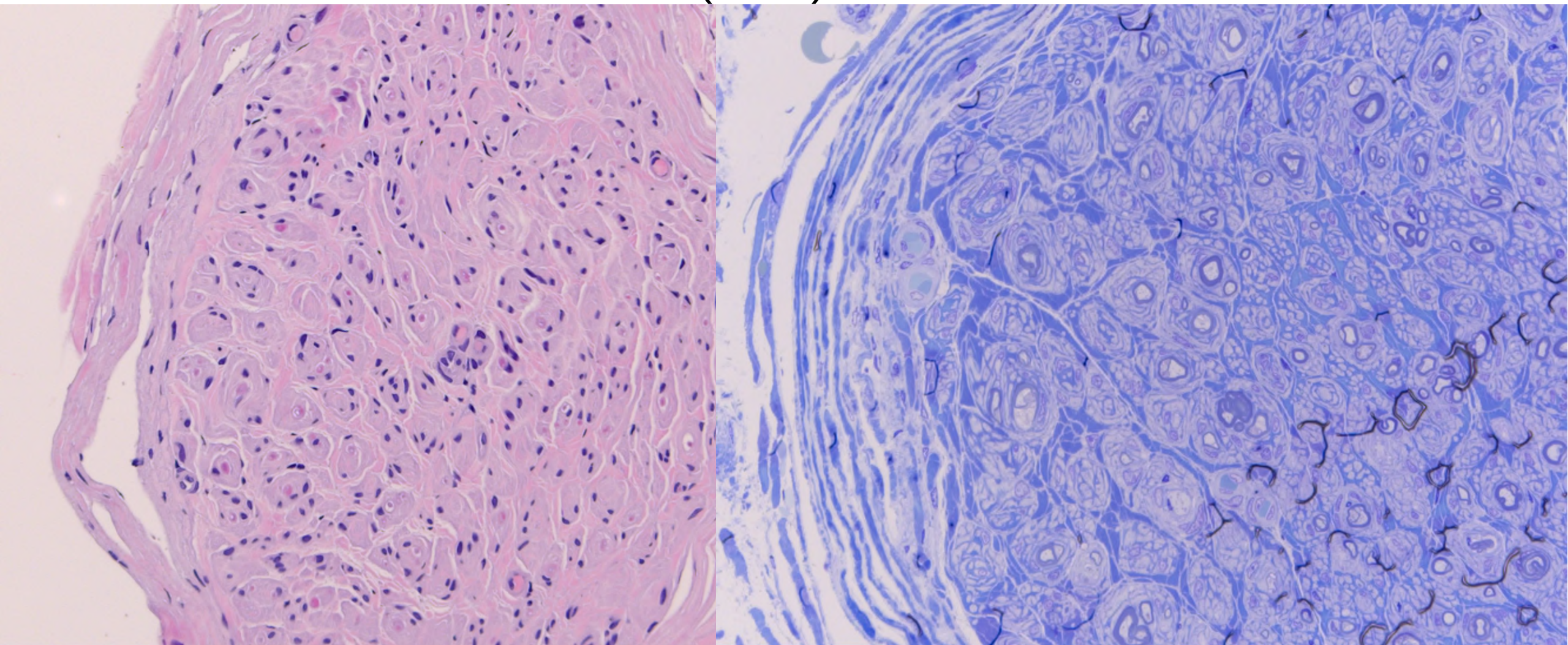


Pressure Palsies (HNPP)

ease

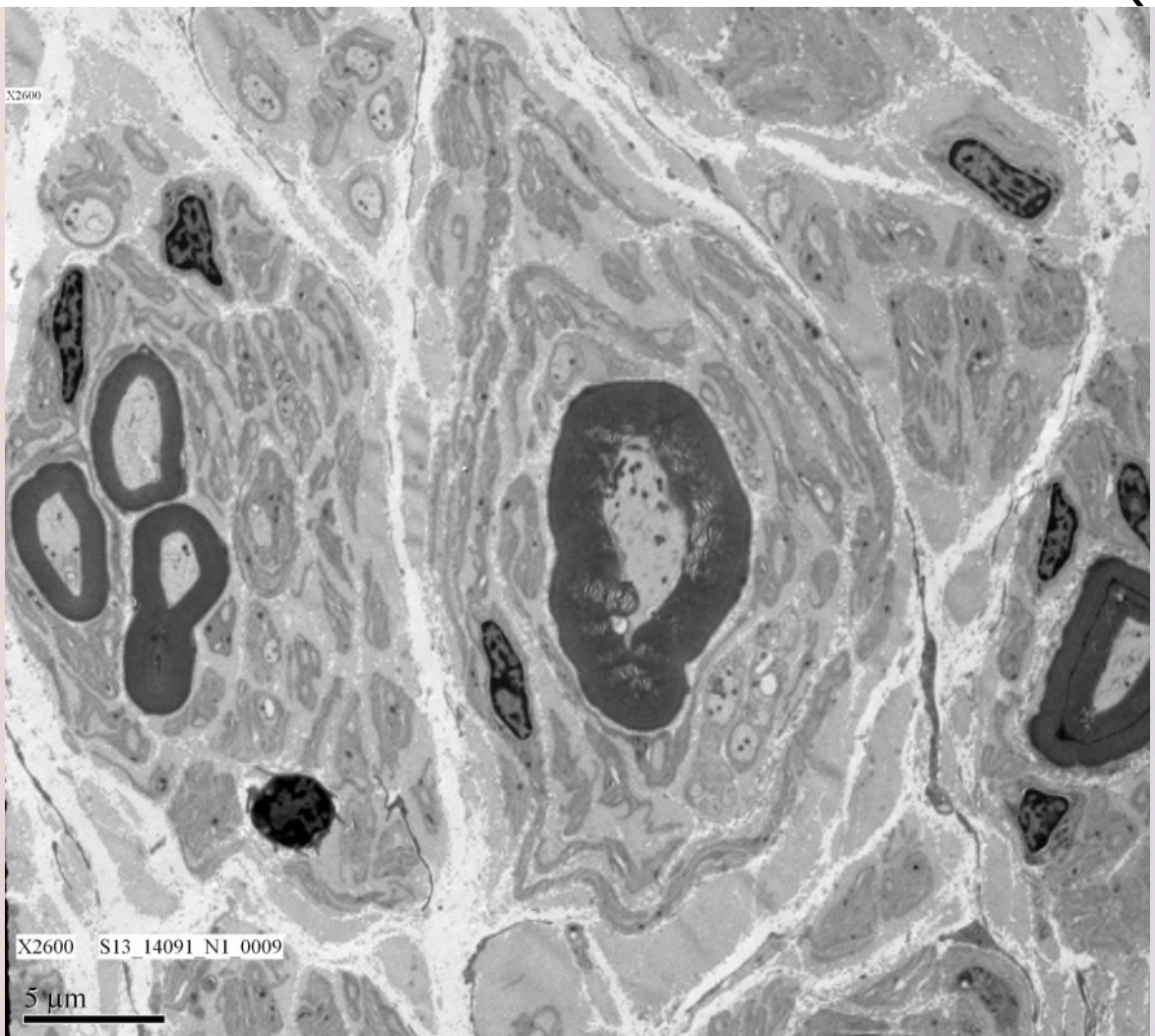
Hereditary diseases / hereditary neuropathies

- Giant axonal neuropathy
- Charcot-Marie-Tooth (CMT)



Hereditary diseases / hereditary neuropathies

- Giant axonal neuropathy
- Charcot-Marie-Tooth (CMT)



Hereditary diseases / hereditary neuropathies

- Giant axonal neuropathy
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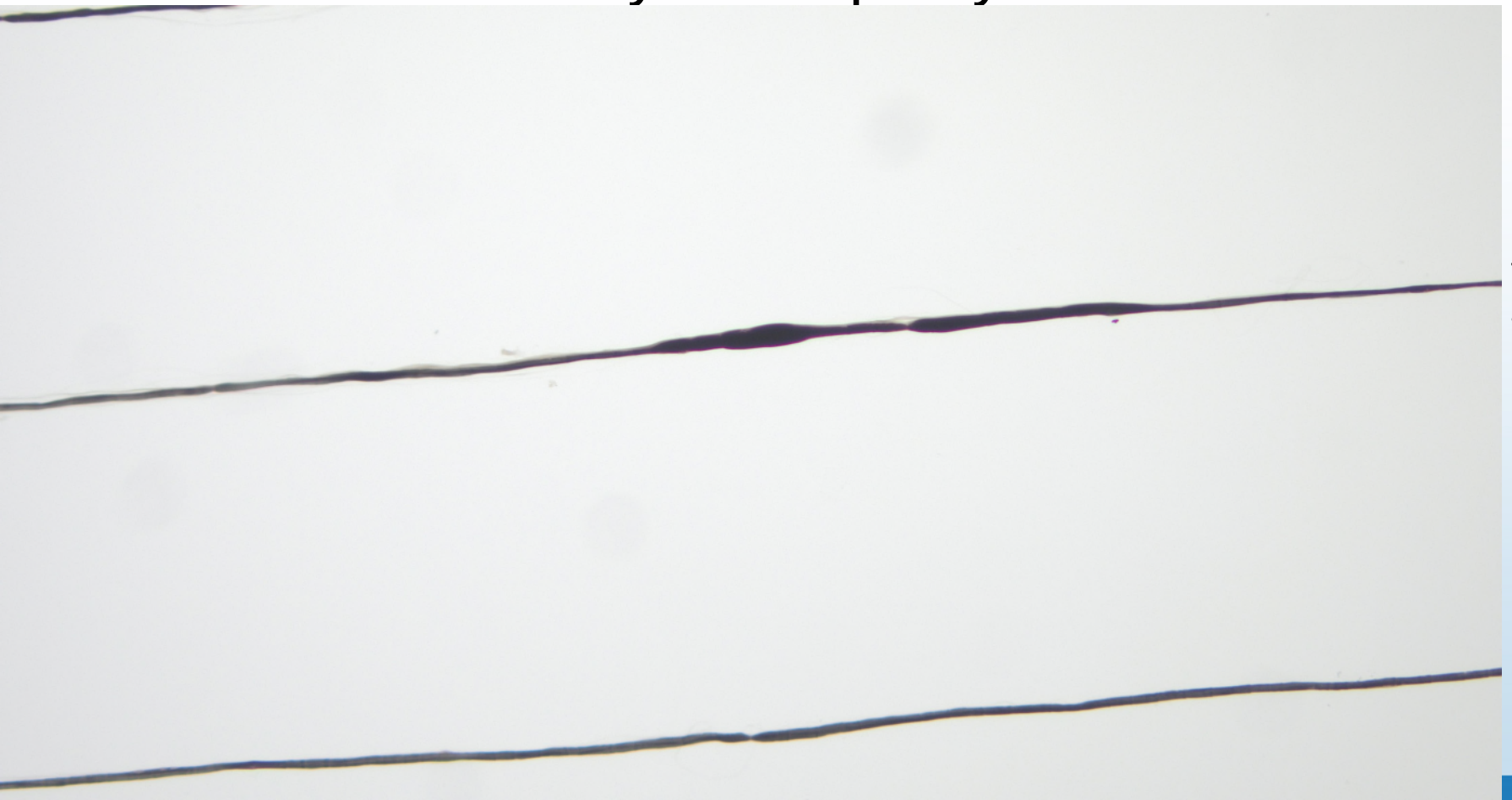
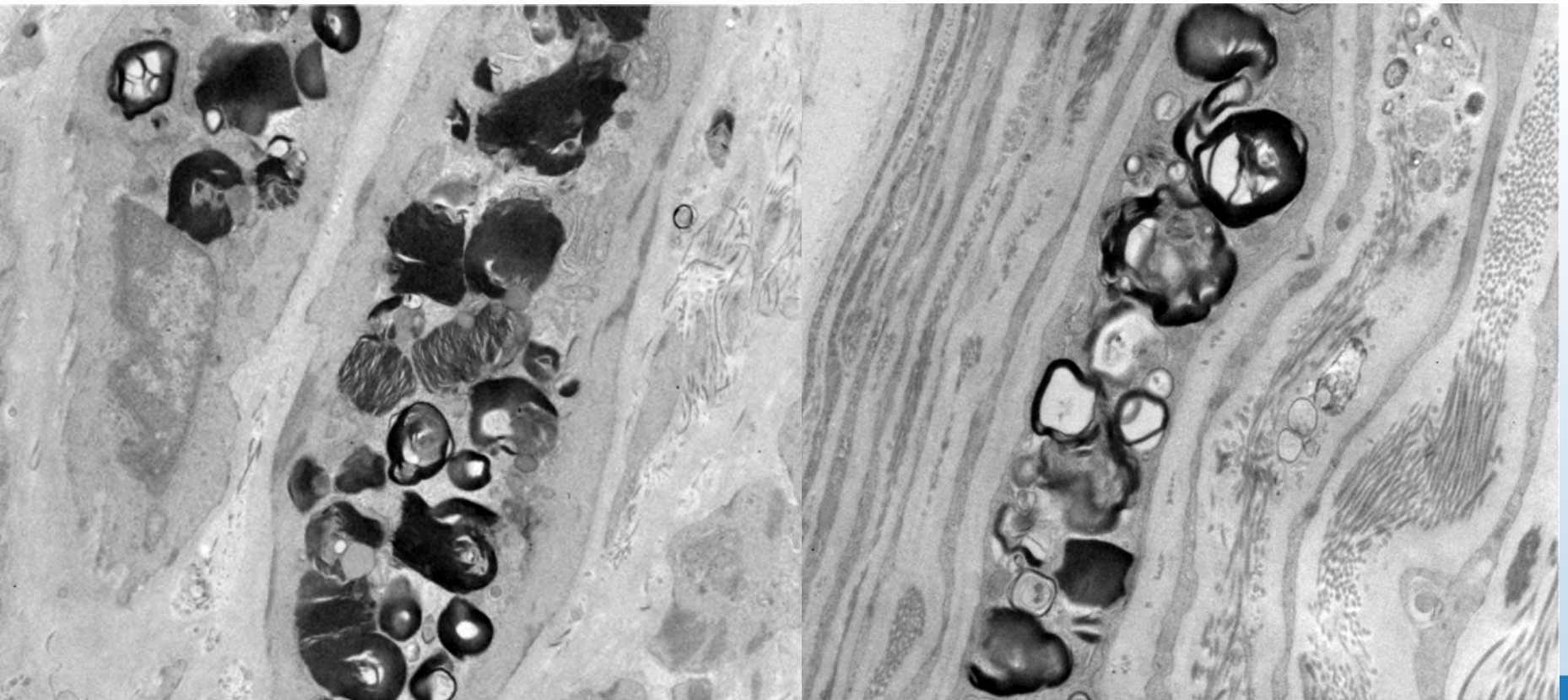
- Hereditary Neuropathy with Pressure Palsies (HNPP)



Tomacula in a biopsy from a patient with HNPP

Hereditary diseases / hereditary neuropathies

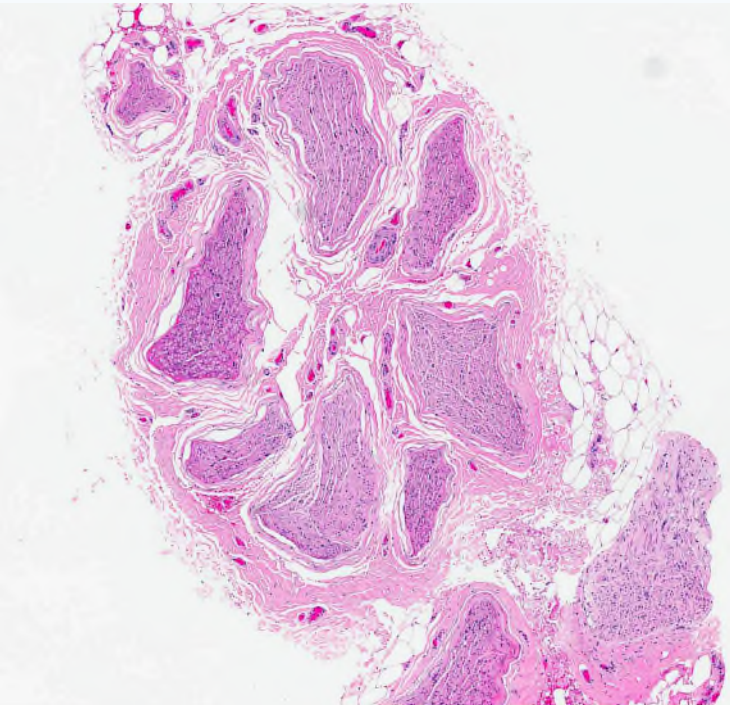
- Giant axonal neuropathy
- Charcot-Marie-Tooth (CMT)
- Hereditary Neuropathy with Pressure Palsies (HNPP)
- Storage diseases / Leukodystrophies

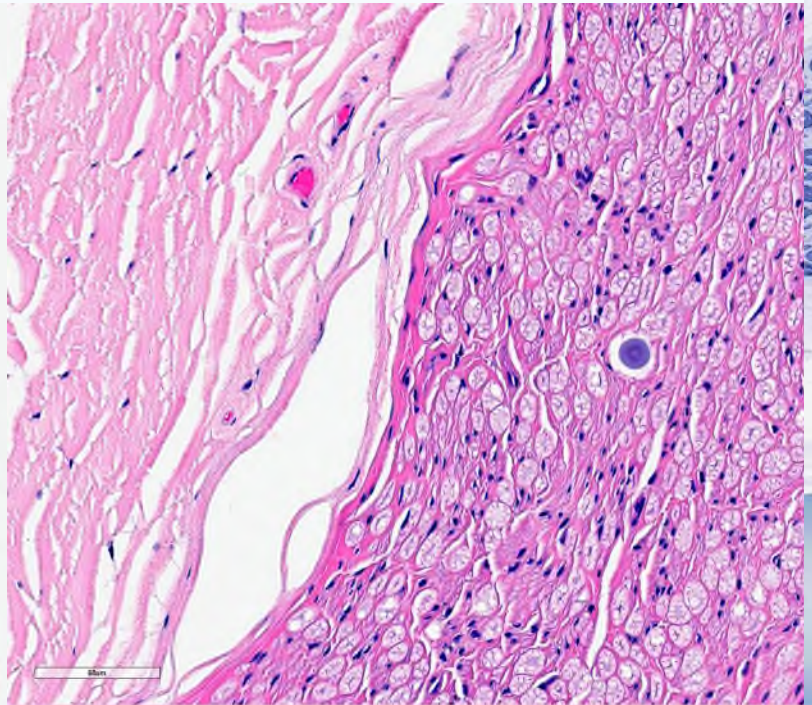


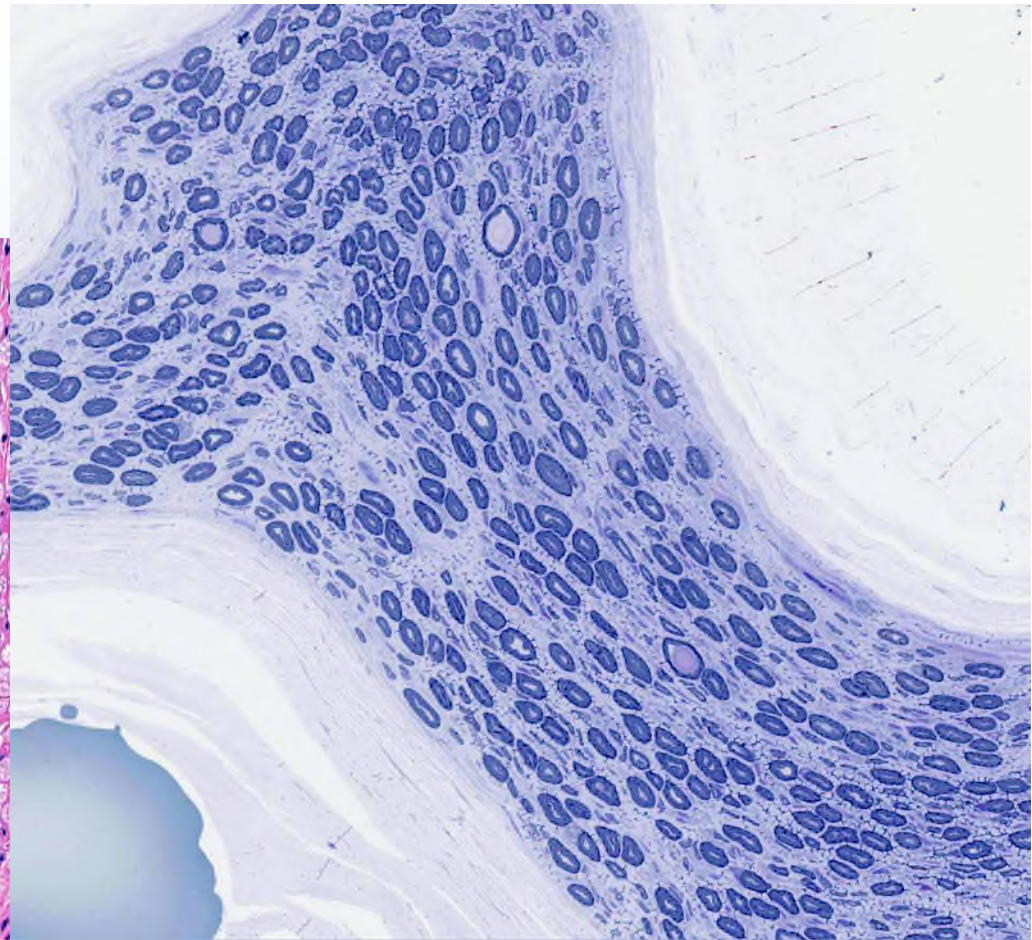
Nerve biopsy from a patient with Fabry disease

Hereditary diseases / hereditary neuropathies

- Giant axonal neuropathy
- Charcot-Marie-Tooth (CMT)
- HNPP
- Storage diseases
- Adult polyglucosan body disease







Hereditary diseases / hereditary neuropathies

- Storage diseases
- Adult polyglucosan body disease
- Leukodystrophies
- Charcot-Marie-Tooth (CMT)
- Hereditary Neuropathy with Pressure Palsies (HNPP)
- Giant axonal neuropathy

=> Diagnosis by genetic testing, not an indication for biopsy

Summary

- Nerve biopsy usually for subacute, progressive cryptogenic vasculitis
- Common specific questions: vasculitis? amyloid?
- Vasculitis
  - Diagnostic criteria for diagnosis
  - Systemic vs NSVN
- Sometimes unusual but distinctive changes
  - Lymphoma, leprosy, onion bulbs, distinctive changes to axons or myelin, storage material