UCSF Health

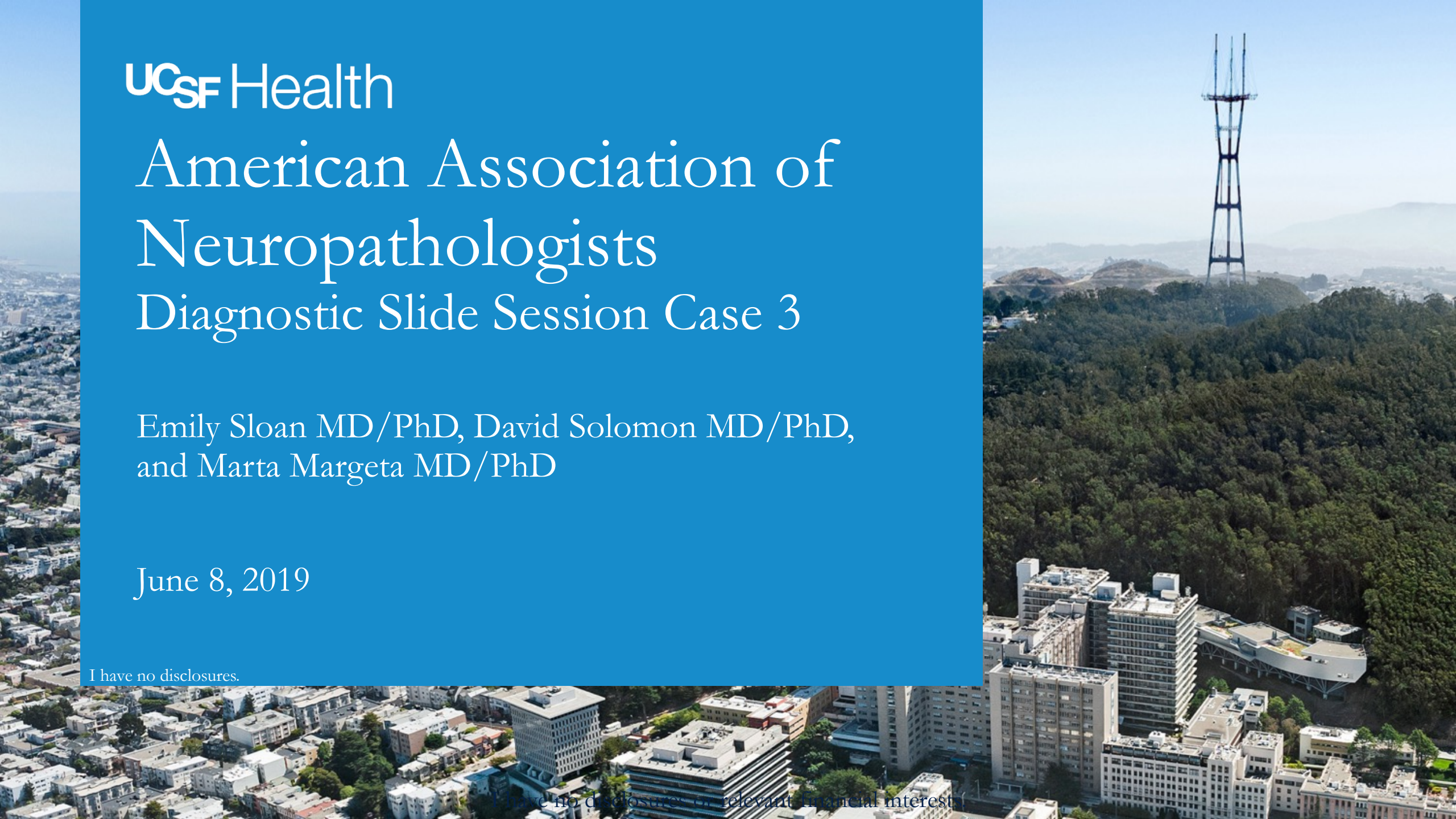
American Association of Neuropathologists

Diagnostic Slide Session Case 3

Emily Sloan MD/PhD, David Solomon MD/PhD, and Marta Margeta MD/PhD

June 8, 2019

I have no disclosures.

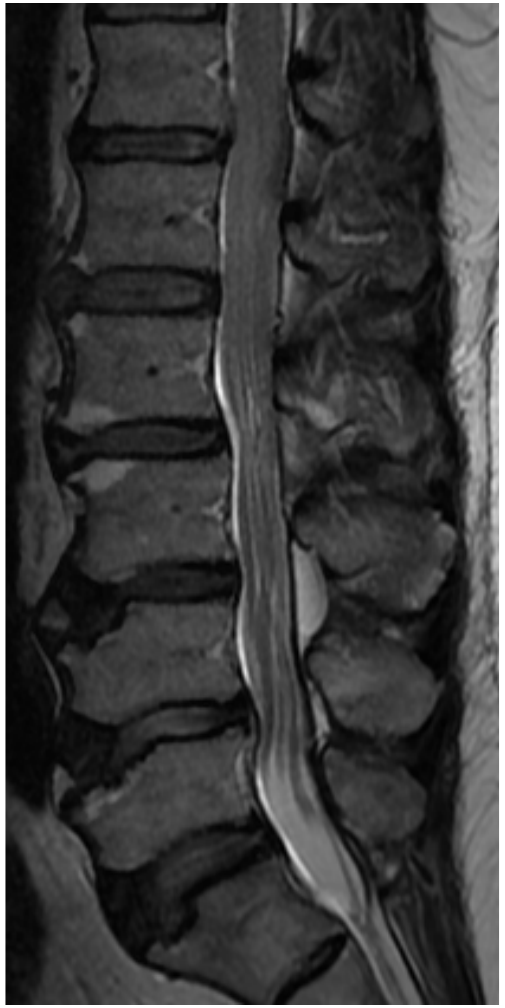


I have no disclosures or relevant financial interests

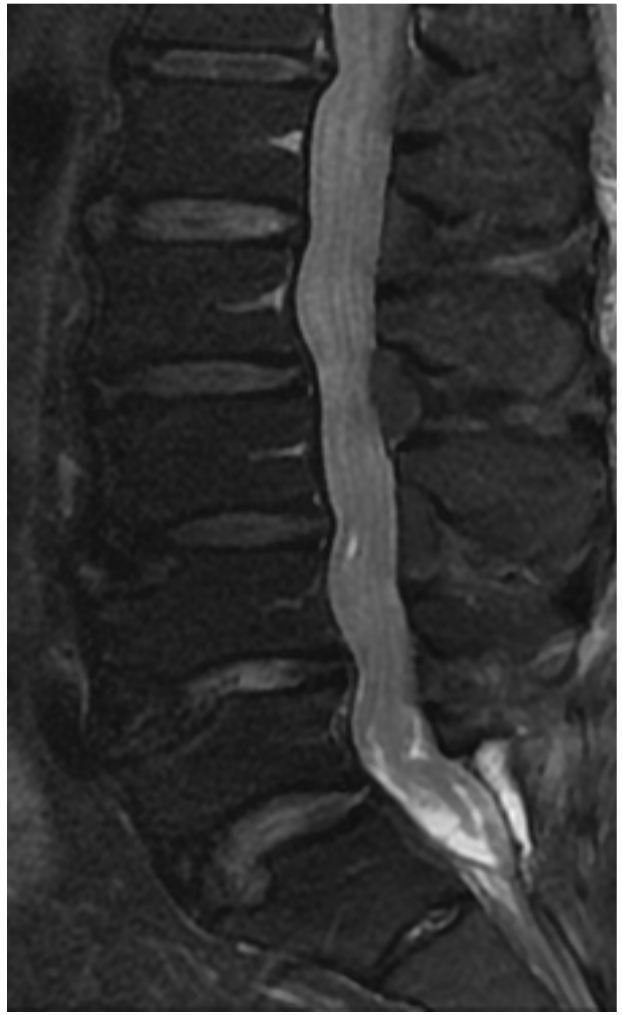
Clinical History

- 61-year-old man with history of non-arteritic ischemic optic neuropathy (NAION) resulting in legal blindness, who presented with 6 month history of radiating lower back pain and leg weakness
- Significant lower extremity, distal-predominant weakness on exam
- Abnormal CSF studies
  - Elevated protein and persistent lymphocytic pleocytosis
  - Positive West Nile Virus IgG/IgM
- EMG/NCS showed evidence for bilateral radiculopathies

Serial Imaging Studies

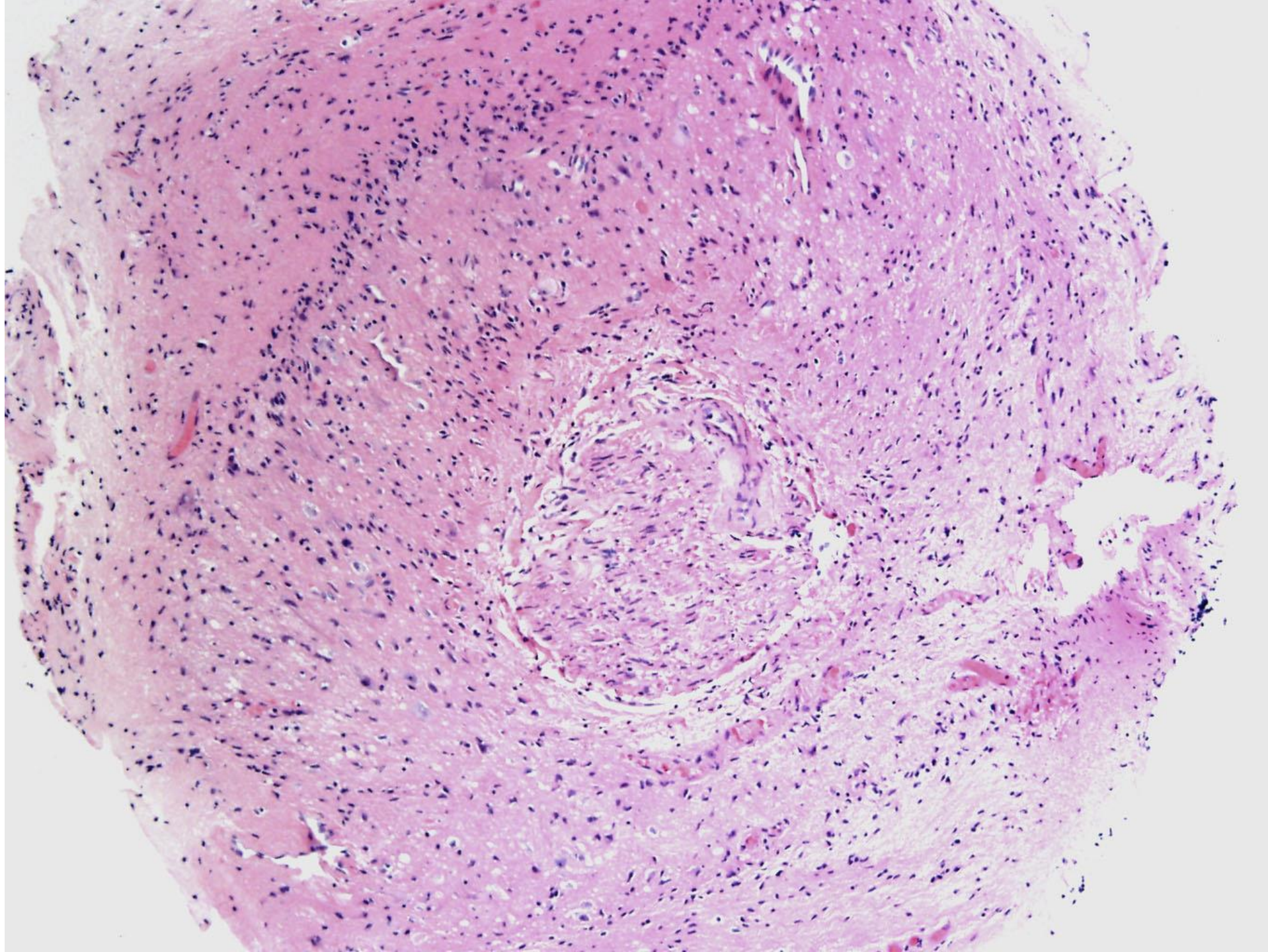


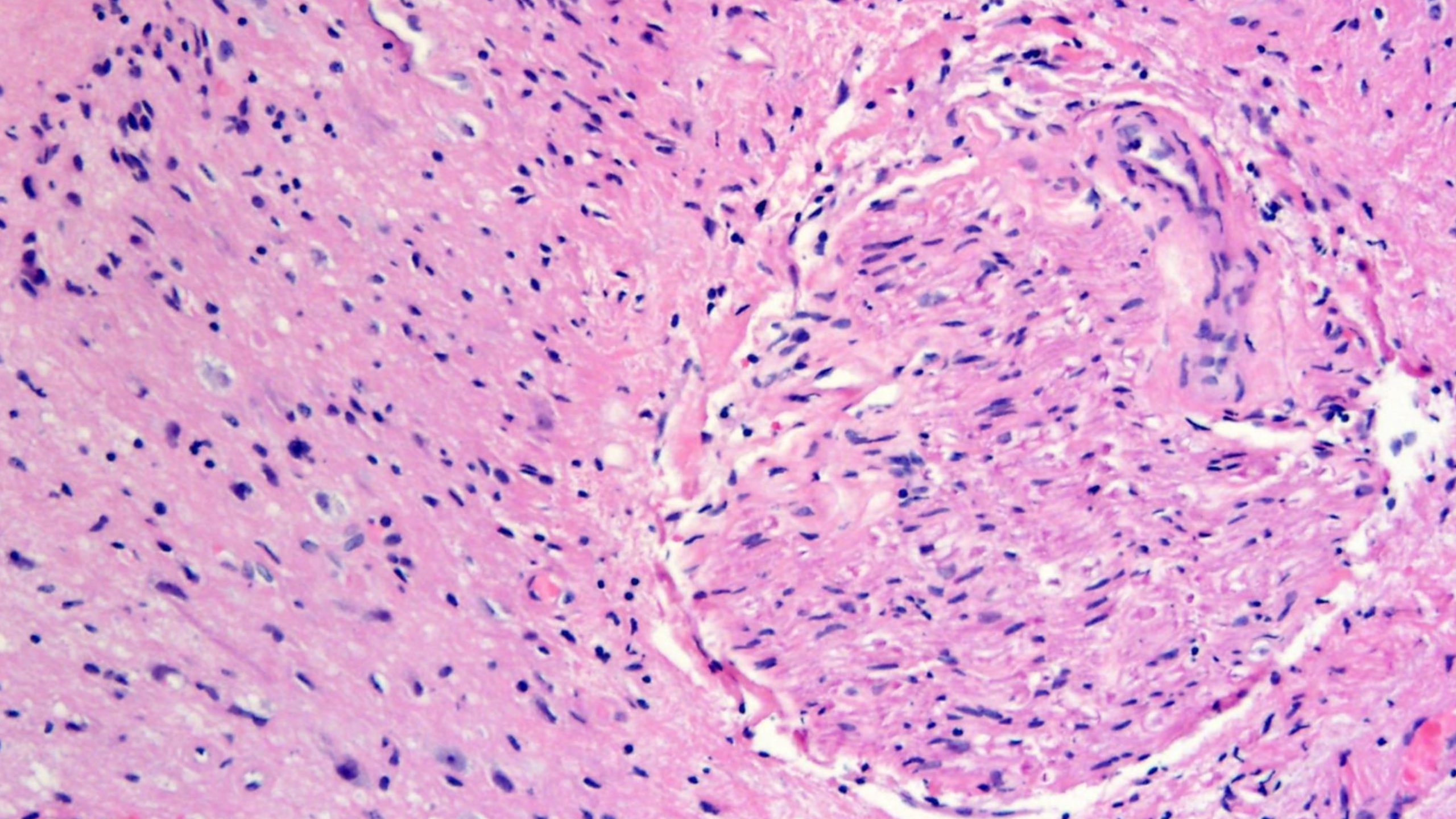
6/2017

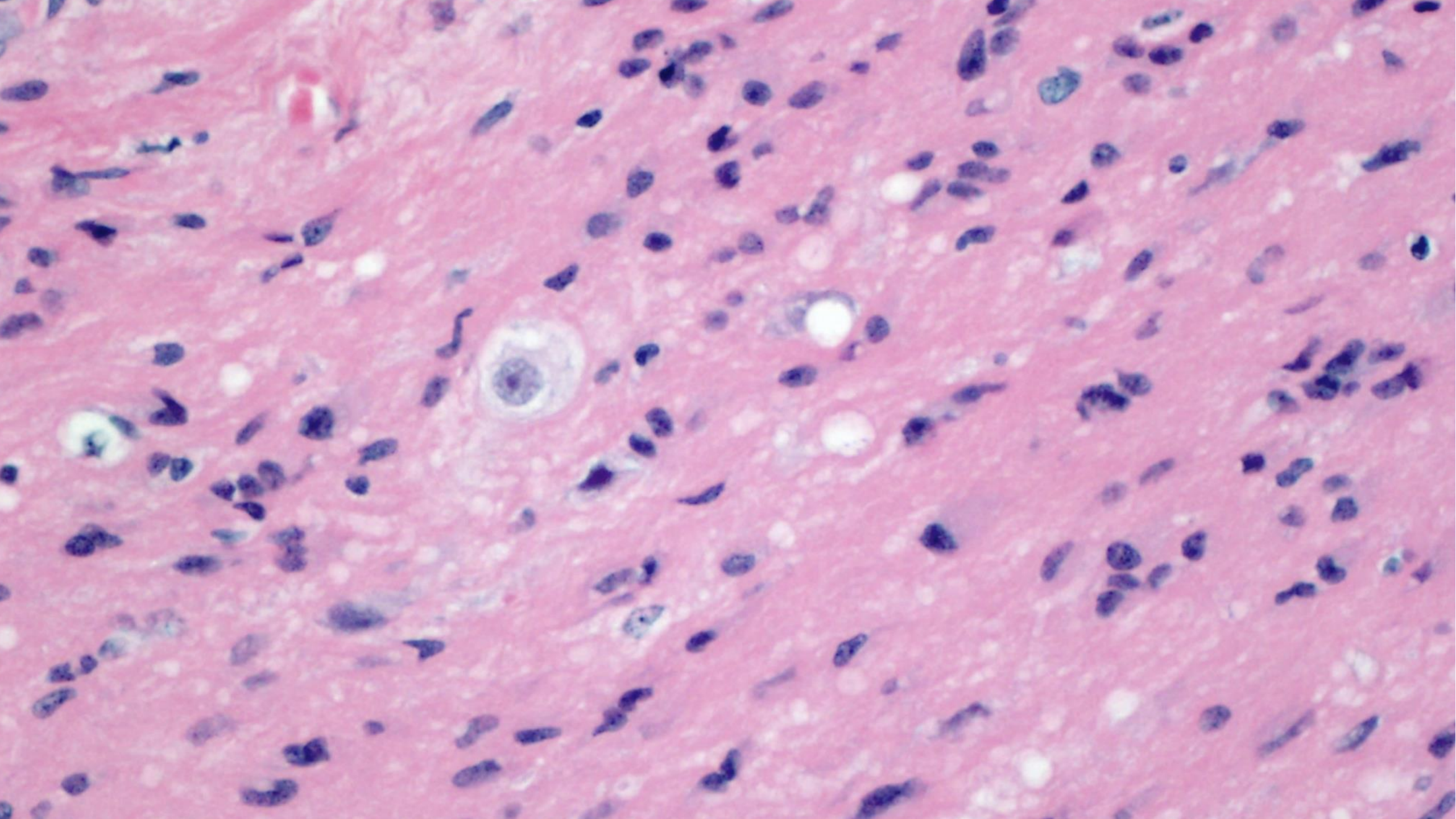


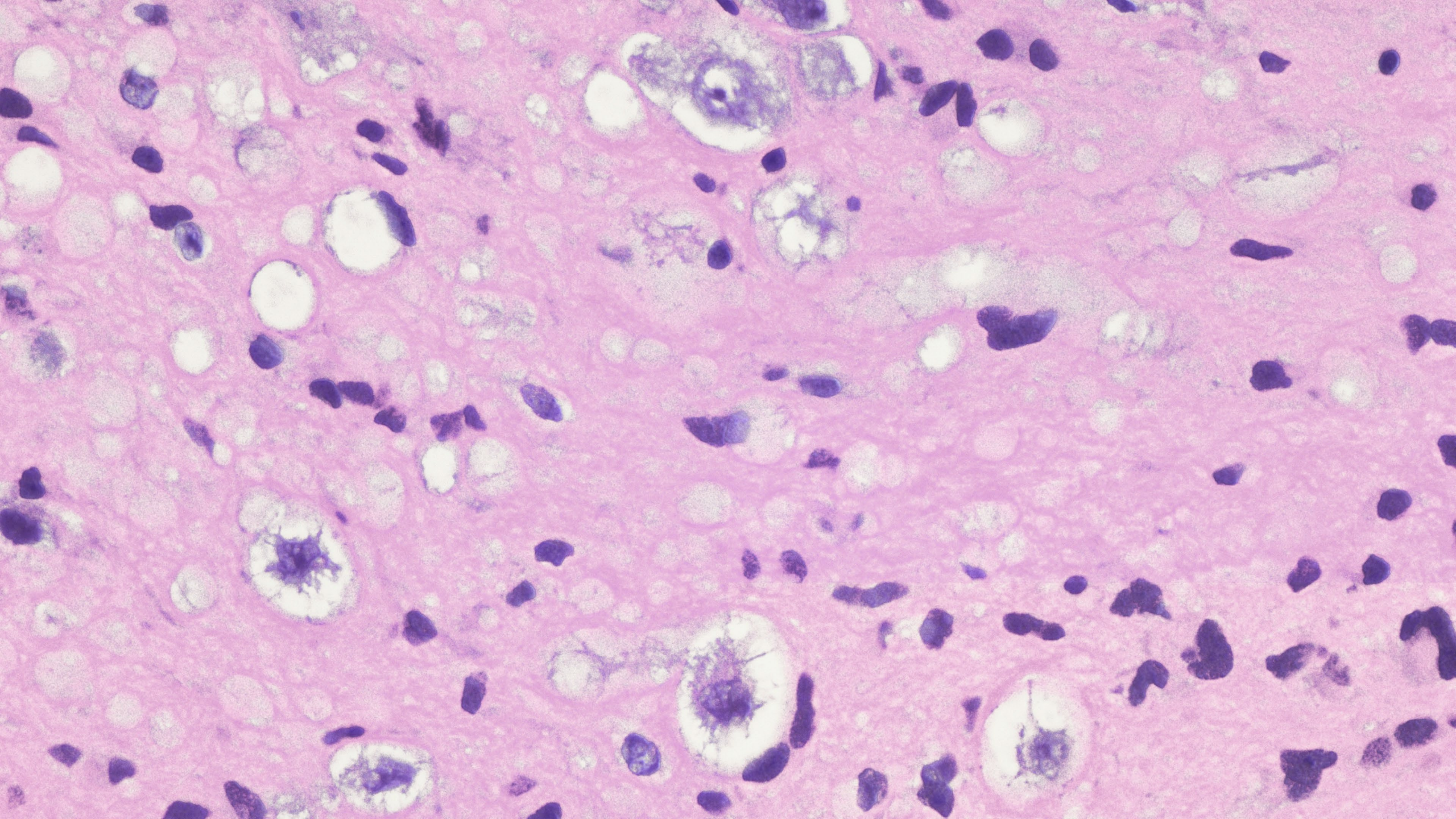
10/2018

A biopsy of the L5/S1 spinal nerve root was performed.



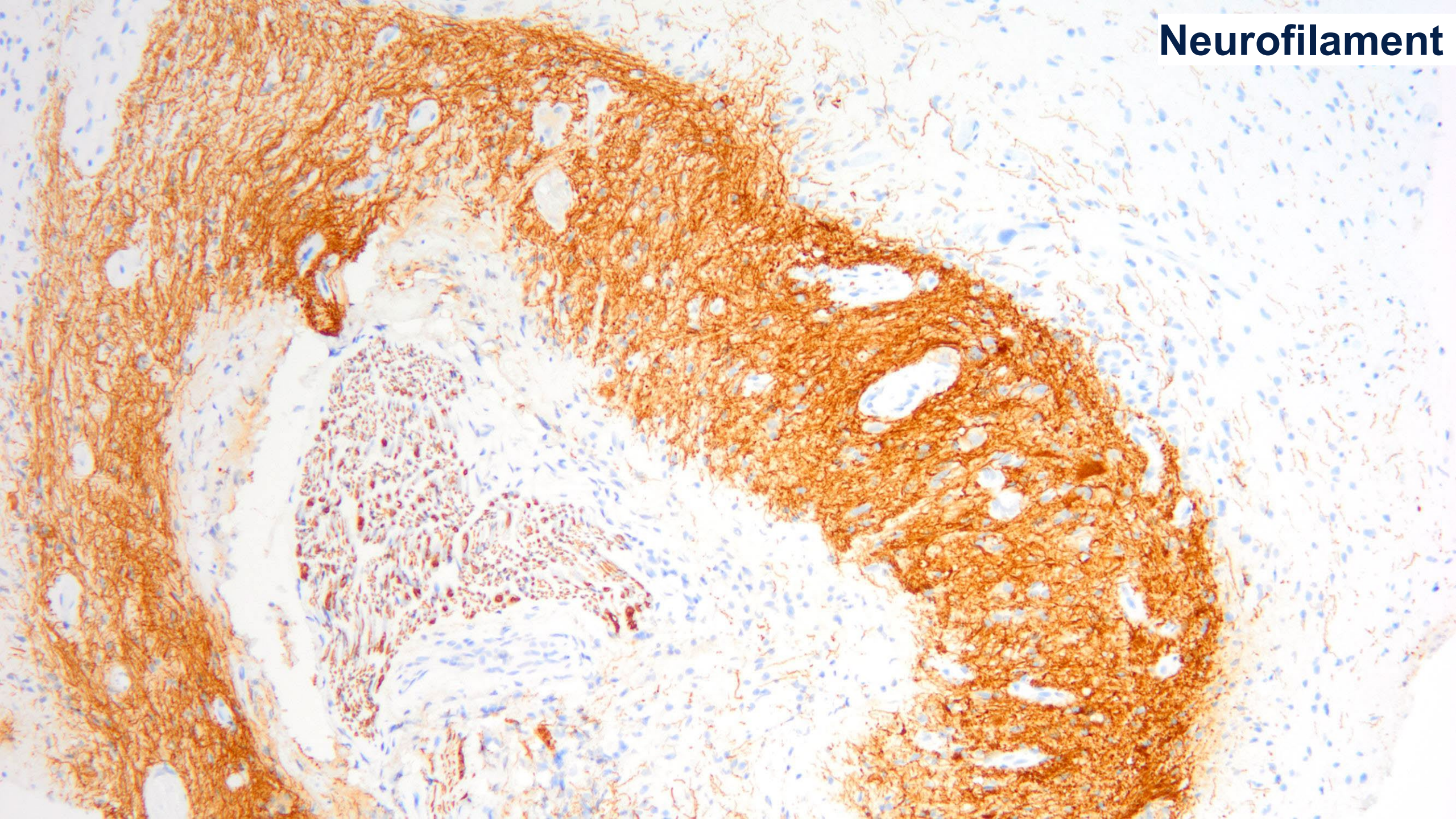


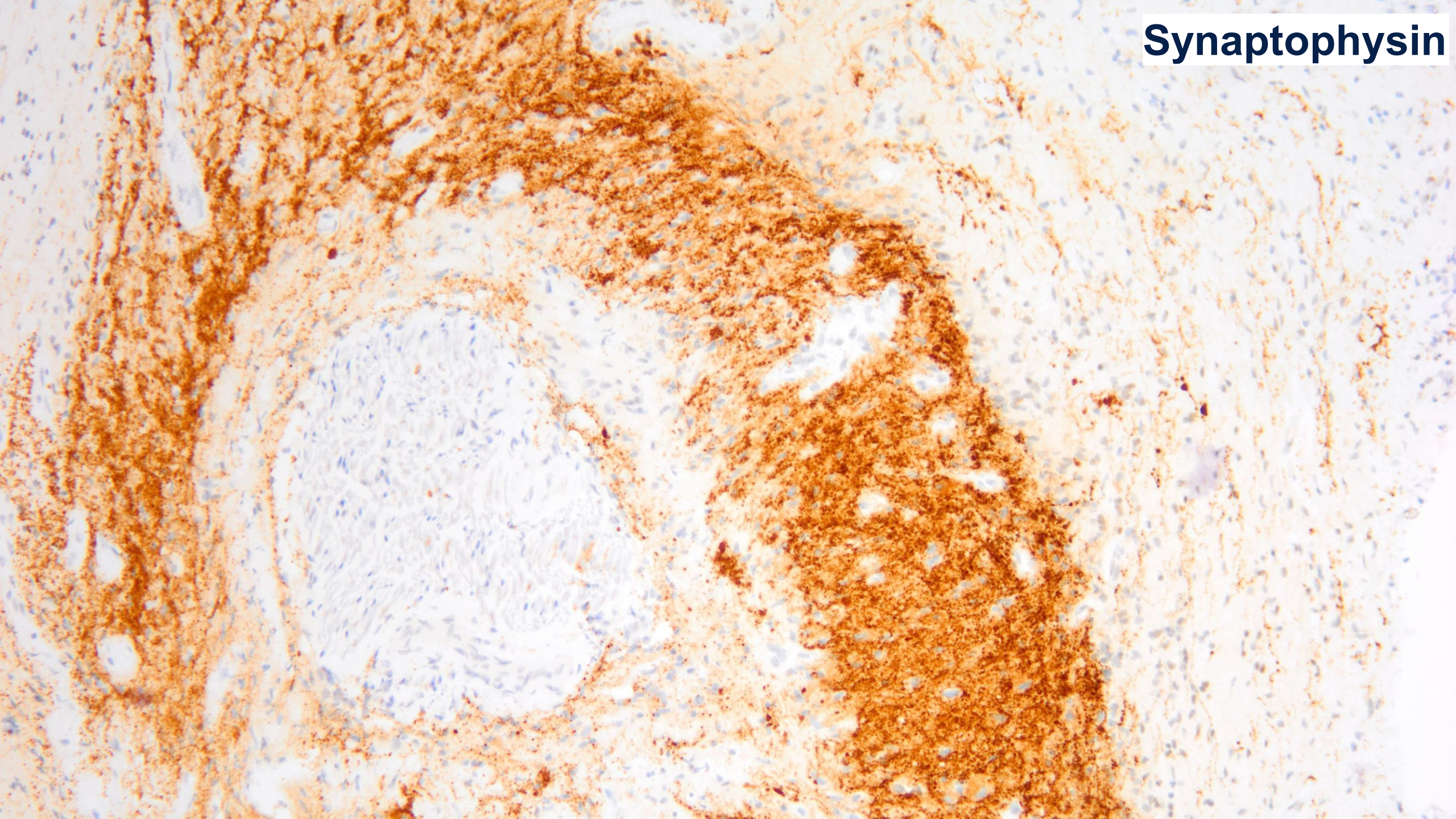


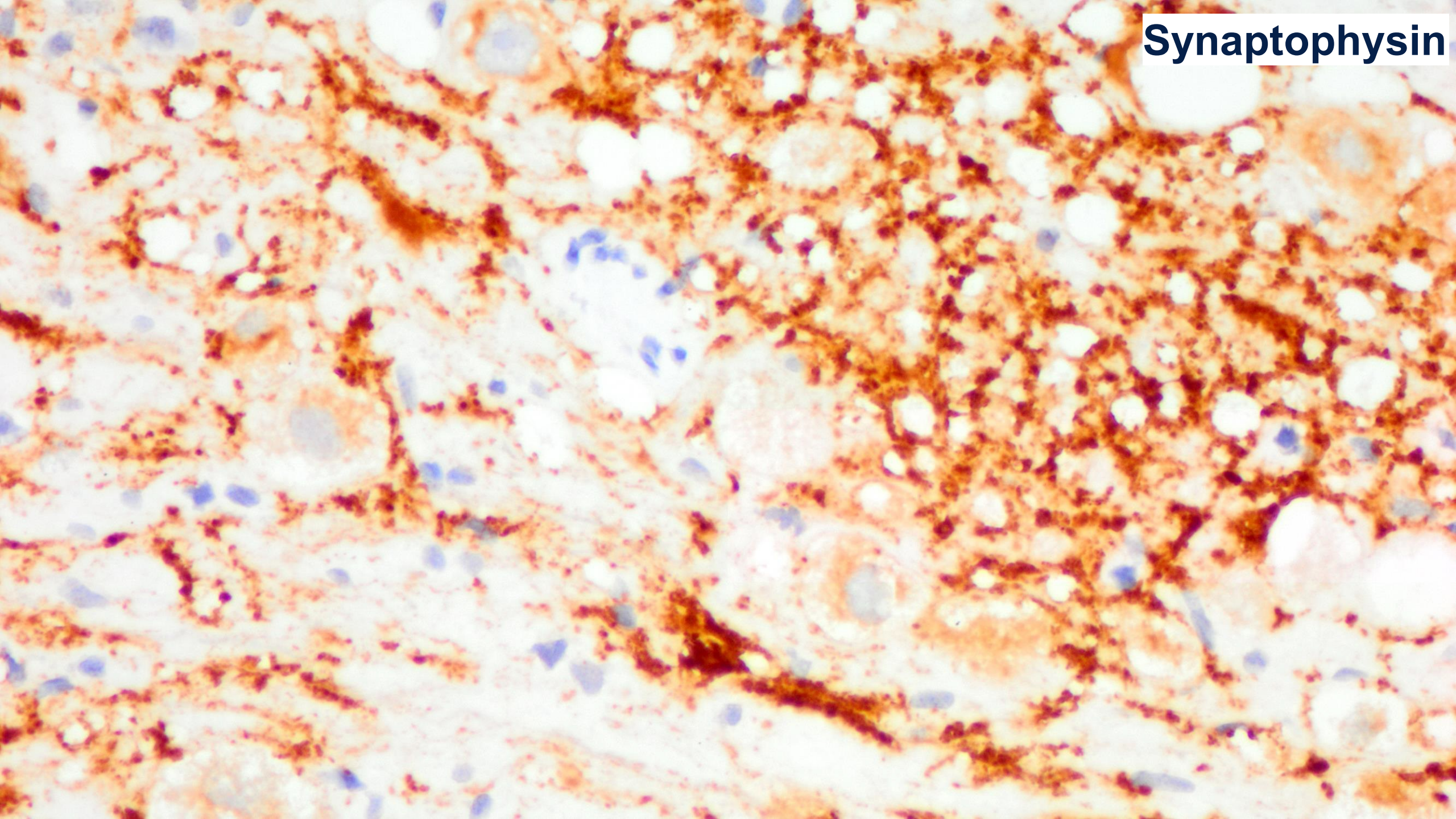


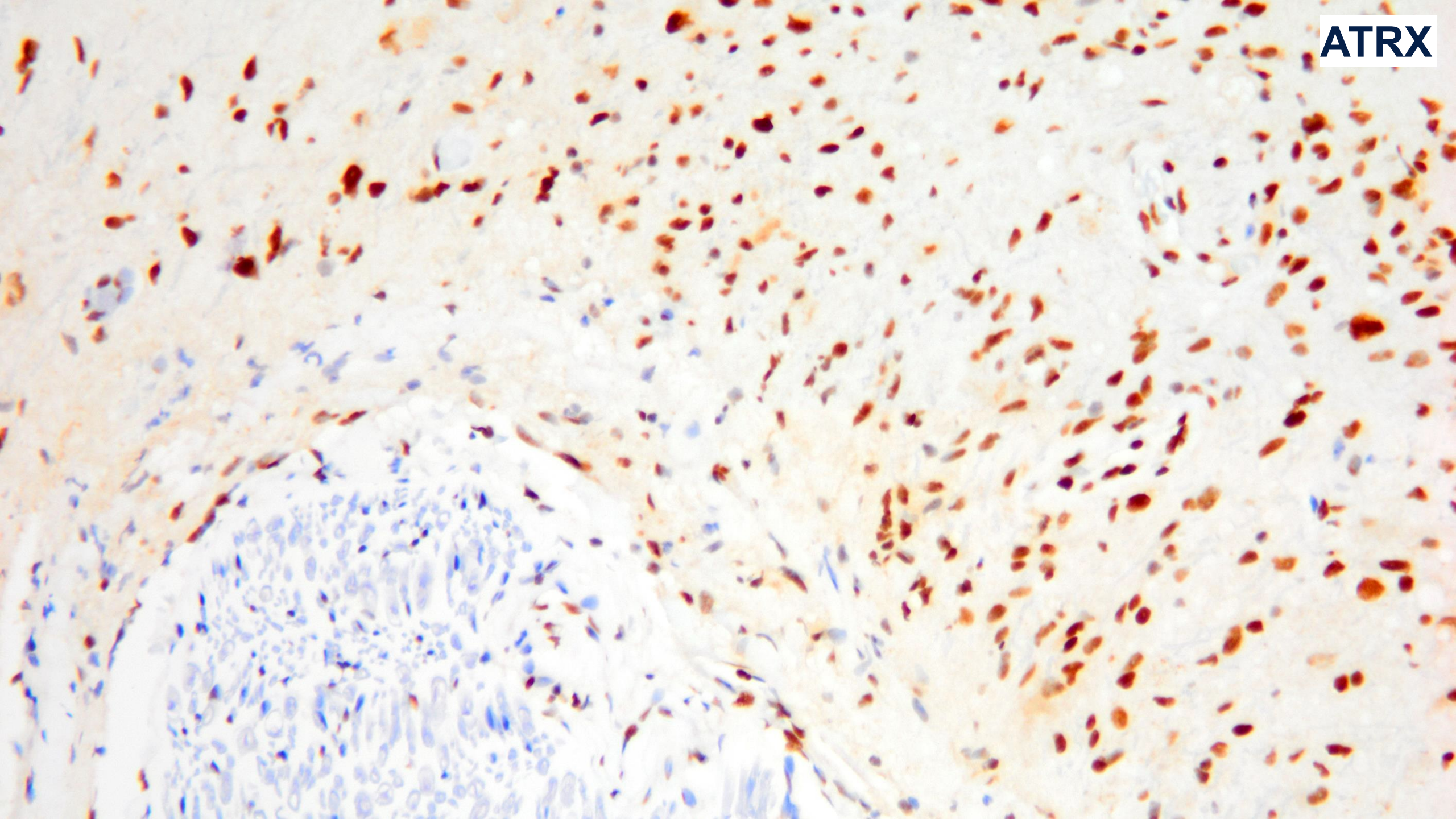
Discussion

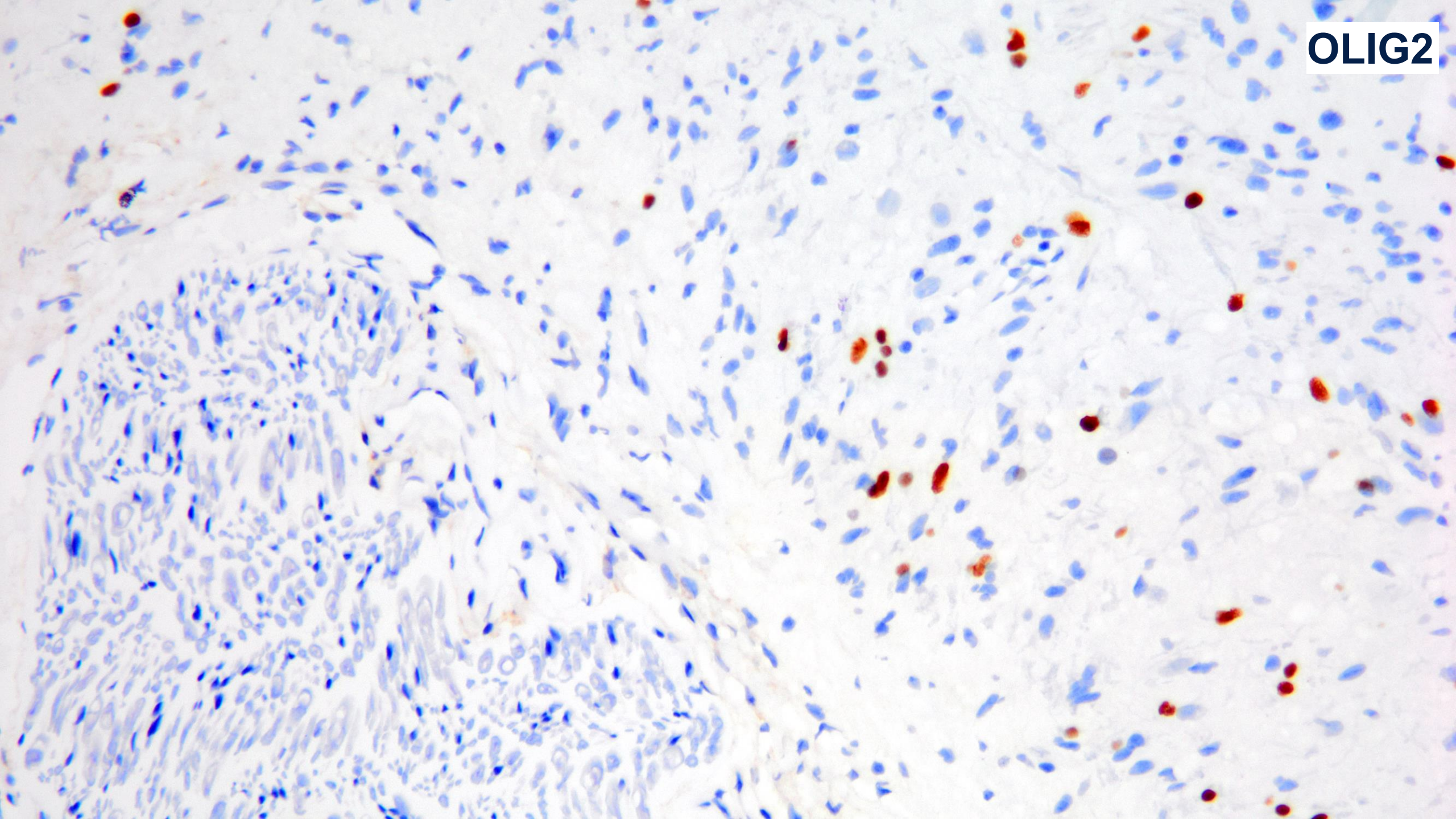
- Differential diagnosis?
- Additional studies?

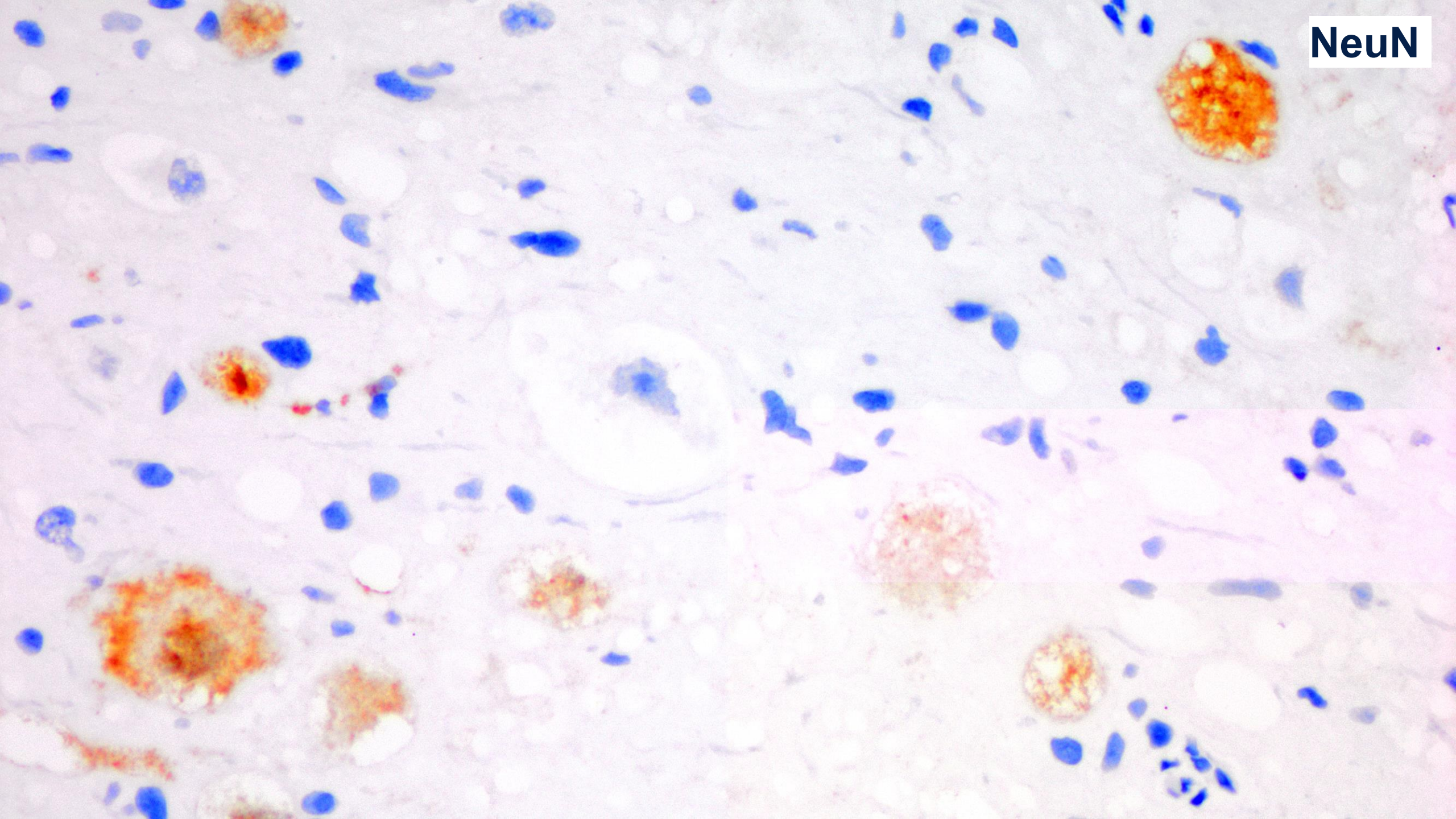

Neurofilament

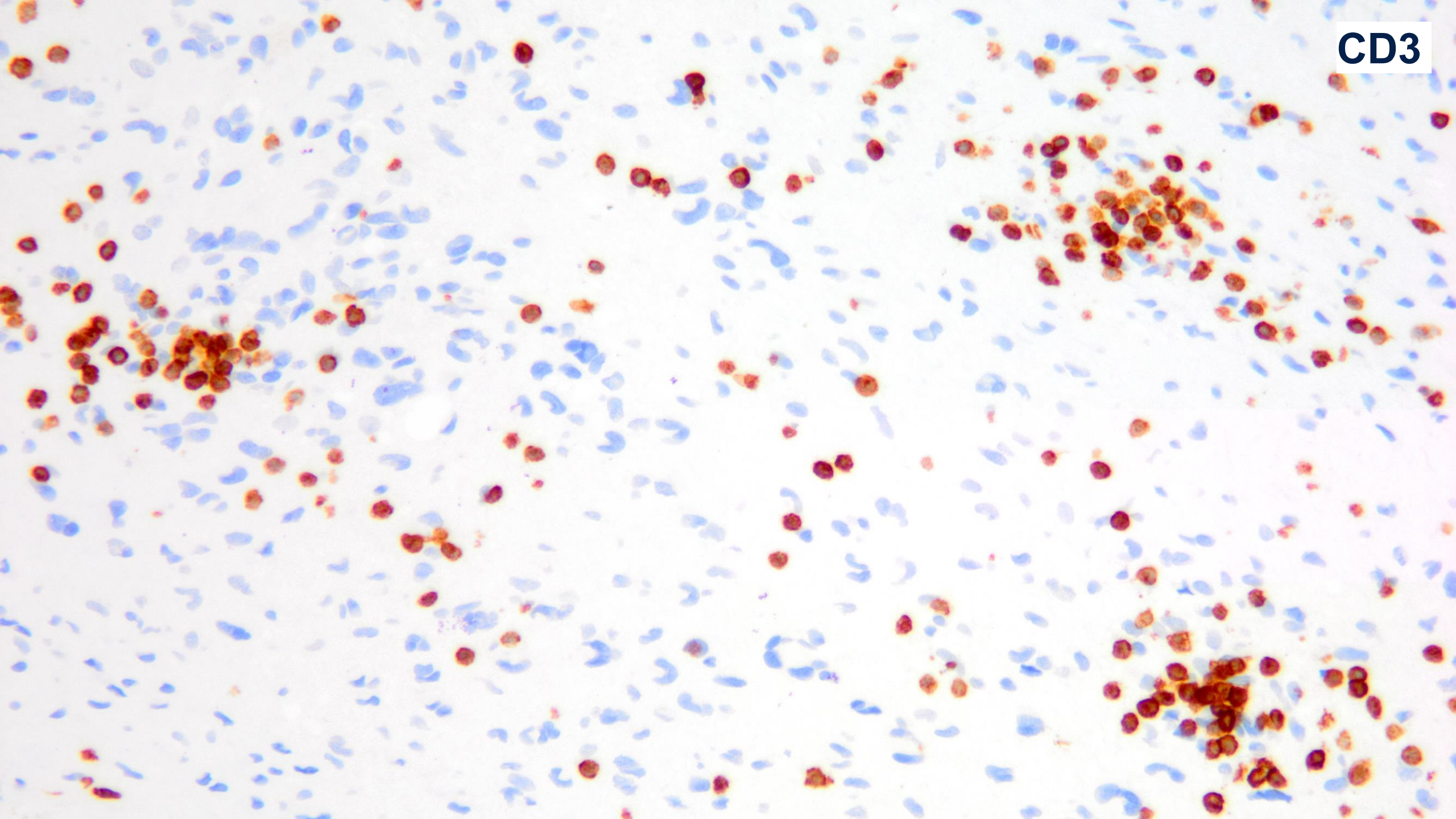

Synaptophysin


Synaptophysin


ATRX


OLIG2


NeuN


CD3

Follow Up Discovery

Patient revealed that he **received intrathecal and intravenous stem cell transfusions** in China and Russia for the purpose of restoring his sight.

UCSF500 Molecular Analysis: Paired lesional tissue and germline sequencing

- No chromosomal gains, losses, focal amplifications or deletions
- No known pathogenic variants including hotspot mutations important in glioma pathogenesis
- **~90 nonsynonymous variants** present in aberrant glioneuronal tissue but not in germline sample
- Vast majority are **single nucleotide polymorphisms** (SNPs) common in human populations
  - Allele frequencies of 20% or 40% likely representing heterozygous and homozygous SNPs

Final diagnosis: L5-S1 Nerve Root Biopsy

Donor-derived glioneuronal proliferation following intrathecal stem cell injection

Donor-derived stem cell glioneuronal lesions

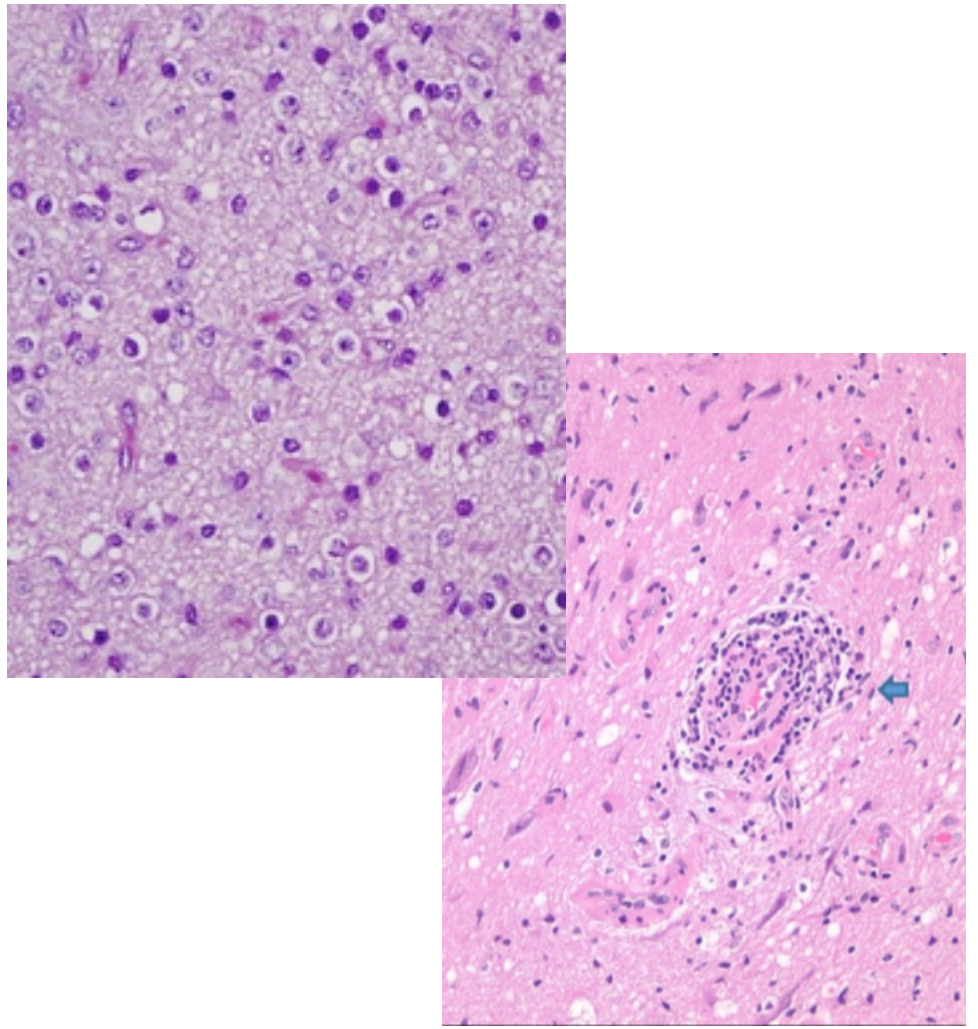
5 previously reported cases

- Age range 13-73
- International travel for intrathecal stem cell injections
  - China, Russia, Mexico, Israel, Argentina
- Protocols unclear but often involved stem cells of fetal origin
- Seeking treatment for variety of disorders
  - Residual deficits from ischemic infarcts
  - Parkinson's disease
  - Ataxia telangiectasia

Amariglio N, et al. *PLOS Medicine.* 2008.

Common Features of Reported Cases

- Intraoperative impression:
  - "Noodle" or "tube-like" encasement
- CSF abnormalities:
  - Lymphocytic pleocytosis, increased protein
- Low-grade glial or glioneuronal proliferation
  - Low Ki-67 labeling index (4/5)
  - Associated chronic inflammatory infiltrate (3/5)
    - Host-derived in one case with microdissection

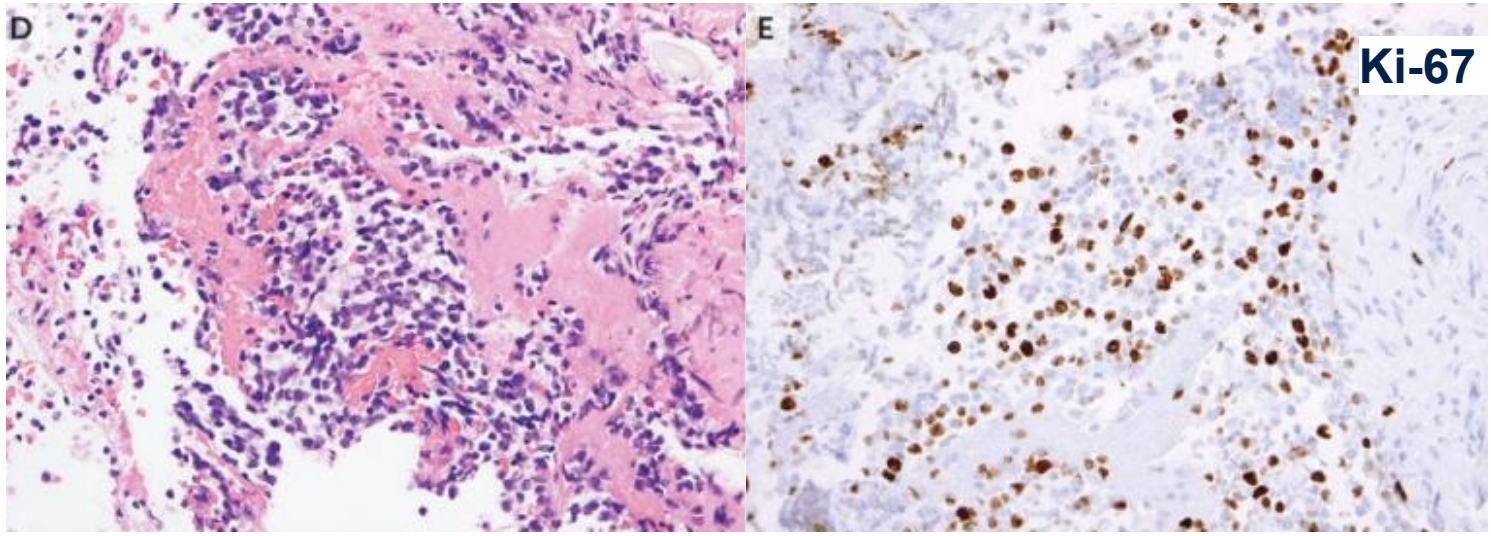


Amariglio N, et al. *PLOS Medicine.* 2008.
Rahangdale R, et al. *Mov Disord Clin Pract.* 2019.

Common Features of Reported Cases

- Non-host origin was confirmed in 4 of 5 cases

- Variety of treatment strategies
  - Observation
  - Radiation
  - Methotrexate +/- radiation
  - Surgical debulking



Berkowitz AL, et al. *N Engl J Med.* 2016.

UCSF Health

Conclusions

- Stem cell therapies can provide hope to patients and potentially address previously untreatable diseases, but carry substantial risks.
- Donor-derived stem cell lesions are one possible complication of experimental stem cell interventions.
- Lumbosacral nerve roots seem to be a permissive environment for stem cell engraftment.
- Pathologists, radiologists and neurologists should be aware of this rare but increasingly reported adverse outcome.

References

- Amariglio N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R, Trakhtenbrot L, et al. (2009) Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient. PLoS Med 6(2): e1000029. PMID: 19226183
- Bauer G, Elsallab M, Abou-El-Enein M. Concise Review: A Comprehensive Analysis of Reported Adverse Events in Patients Receiving Unproven Stem Cell-Based Interventions. Stem Cells Transl Med. 2018.
- Berkowitz AL, Miller MB, Mir SA...Chi JH. Glioproliferative Lesion of the Spinal Cord as a Complication of "Stem-Cell Tourism". N Engl J Med. 2016 Jul 14;375(2):196-8. PMID: 27331440
- Connolly R, O'Brien T, Flaherty G. Stem cell tourism--a web-based analysis of clinical services available to international travellers. Travel Med Infect Dis. 2014 Nov-Dec;12(6 Pt B):695-701.
- Douglas Ney, Vera Fridman, Mark Ewalt, B K Kleinschmidt-DeMasters. Chimeric Spinal Cord Glioproliferative Lesion Following Intrathecal Fetal Stem Cell Infusion. Neuro-Oncology, Volume 20, Issue suppl_6, November 2018, Pages vi241–vi242.
- Hurst RW, Bosch EP, Morris JM, Dyck PJ, Reeves RK. Inflammatory hypertrophic cauda equina following intrathecal neural stem cell injection. Muscle Nerve. 2013 Nov;48(5):831-5. doi: 10.1002/mus.23920. PMID: 23740462
- Lee BS, Achey RL, Yeaney GA, Bosler DS, Aly Z, Ontaneda D, Morren J, Benzel EC. Stem cell injection-induced glioneuronal lesion of the cauda equina. Neurology. 2018 Mar 27;90(13):613-615. PMID: 29476035
- Rahangdale R, Rana S, Prakash P, Ali M, Flaherty M, Synowiec A, Baser S, Scott T. Glioneuronal Growth Infiltrating Lumbosacral Nerve Roots Following Intrathecal Stem Cell Injections Highlighting Perils of Stem Cell Tourism. Movement Disorders Clinical Practice. 2019 Mar 12;6(4):324-326. PMID: 31061842

University of California
San Francisco