Aerotoxic syndrome in pilots: a post-mortem examination

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- Introduction
  - Aerotoxic syndrome
  - Organophosphate intoxication
  - Does it exsist?
- Materials and Methods
- Results
- Discussion

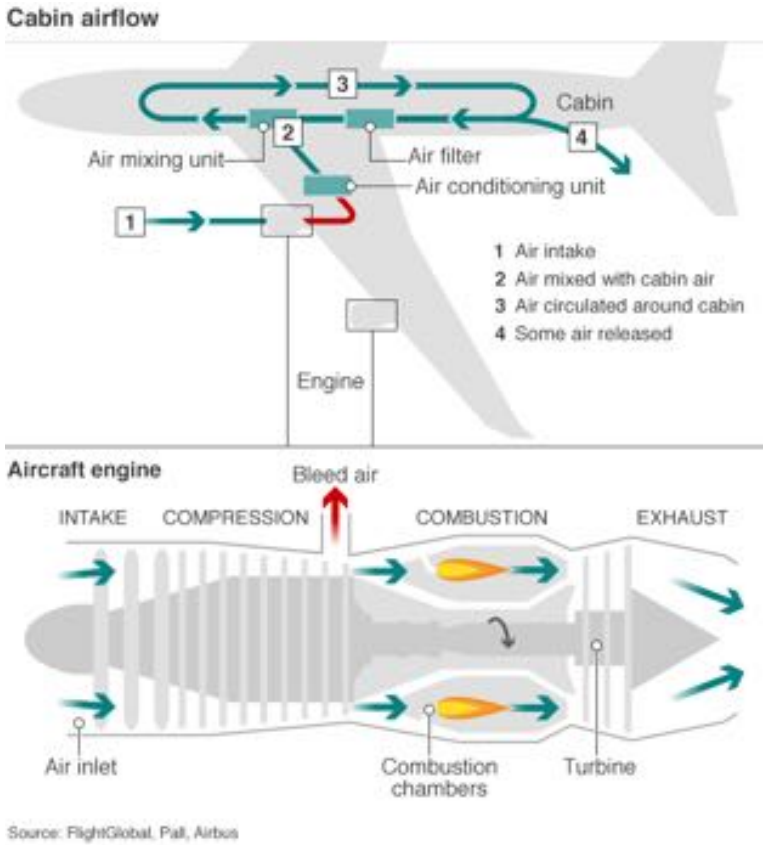
Aerotoxic syndrome

- Disorientation
- Loss of balance
- Lightheadedness
- Headaches
- Fatigue
- Blurred vision or tunnel vision
- Cognitive problems
  - Concentration
  - Memory loss
- Chest pain
- Palpitations
- Joint pain
- Muscle weakness.

Winder, C., Balouet, J.-C. (2000). Aerotoxic syndrome: Adverse health effects following exposure to jet oil mist during commercial flights. In: I. Eddington, Ed. Towards a safe and civil society, Proceedings of International Congress on Occupational Health, Held in Brisbane, Australia, 4-6 september 2000

Aerotoxic syndrome

- Airsupply to cockpit
  - Pressurized and temperature in engine
  - Fumes from engine oil
- Engine oil
  - Synthetic ester base
  - Anti-wear additives
- Organophosphates
  - Tricresyl phosphate (TCP)
- Fume events
  - 0.02% to 0.5% of flights



Megson, D., Ortiz, X., Jobst K. J., Reiner, E. J., Mulder, M. F. A., Balouet, J.-C. (2016) A comparison of fresh and used aircraft oil for the identification of toxic substances linked to aerotoxic syndrome. *Chemosphere 158, 116-123*

Organophosphate intoxication

ACUTE EFFECTS

CHOLINERGIC TOXICITY

- Large amounts of organophosphate
- Acetylcholinesterase (AChE) irreversibly inhibited
- Miosis
- Tremors
- Increased sweating and salivation
- Central nervous system symptoms,
  - dizziness, convulsions and coma.
- The central respiratory centers inhibition
  - death

LATE EFFECTS

ORGANOPHOSPHATE-INDUCED DELAYED POLYNEUROPATHY (OPIDP)

- Often in TCP intoxication
- Symptoms arise 2-3 weeks after exposure
- Targeting of Neuropathy Target Esterase (NTE)?
- Tingling of hands and feet
- Sensory loss
- Progressive muscles weakness
- Ataxia
- Neuropathology:
  - CNS: distal axonal degeneration, axonal loss, neuronal loss in pyramidal tracts and dorsal columns
  - PNS: distal axonal degeneration

Costa, L. G. (2018) Organophosphorus compounds at 80: Some old and new issues. *Toxicological sciences 162(1), 24-35*

Organophosphate intoxication

- Chronic Organophosphate-Induced Neuropsychiatric Disorders (COPIND)
- Can occure without cholinergic toxicity
- Mechanism unknown
- Chronic fatigue
- Mood changes
  - Anxiety, depression or psychotic symptoms
- Peripheral neuropathy
- Extrapyramidal symptoms
- Cognitive symptoms
  - Concentration, memory, attention, information processing and reaction time

Jokanovic, M. (2018) Neurotoxic effects of organophosphorus pesticides and possible association with neurodegenerative diseases in man: A review. *Toxicology 410, 125-131*

Organophosphate intoxication

- Auto-antibodies
  - Neurofilament protein (NFP)
  - Tau protein
  - Tubulin
  - Myelin basic protein (MBP)
  - Microtubule-associated protein 2 (MAP-2)
  - Glial fibrillary acidic protein (GFAP)
  - S-100B

- multiple sclerose (MBP)
- Alzheimer's disease (S-100B, GFAP)
- Parkinson's disease (SNCA, MAG)
- Traumatic brain injury (MBP, GFAP, S-100B).

El Rahman, H. A. A., Salama, M., El-Hak, S. A. G., El-Harouny, M. A., ElKafrawy, P., Abou-Donia, M. B. (2018) A panel of autoantibodies against neural proteins as peripheral biomarker for pesticide-induced neurotoxicity. *Neurotoxicity research 33, 316-336*

Berger, T., Rubner, P., Schautzer, F., Egg, R., Ulmer, H., Mayringer, I., Dilitz, E., Deisenhammer, F., Reindl, M. (2003) Antimyelin antibodies as predictor of clinically definite multiple sclerose after a first demyelinating event. *New England journal of medicine 349, 139-145*

Colasanti, T., Barbati, C., Rosano, G., Malorni, W., Ortona, E. (2010) Autoantibodies in patients with Alzheimer's disease: pathogenetic role and potential use as biomarkers of disease progression. *Autoimmunity reviews 9, 807-811*

Tansey, M. G., Romero-Ramos, M. (2018) Immune system responses in Parkinson's disease: Early and dynamic. *European journal of neuroscience 1-20*

Papuc, E., Rejdak, K. (2017) Anti-MAG autoantibodies are increased in Parkinson's disease but not in atypical parkinsonism. *Journal of neural transmission 124, 209-216*

Kobeissy F, Moshourab RA. Autoantibodies in CNS Trauma and Neuropsychiatric Disorders: A New Generation of Biomarkers. In: Kobeissy FH, editor. Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects. Boca Raton (FL): CRC Press/Taylor & Francis; 2015. Chapter 29

Case report

- 43-year old male pilot
- Extensive history of complaints ascribed to aerotoxic syndrome
- Found dead in hotel room
- Cause of death
  - Pentobarbital intoxication
  - Lymfocytic myocarditis and narrowing of coronary arteries
  - Combination of the two

Abou-Donia, M. B., Goot, F. R. W. van der, Mulder, M. F. A. (2014) Autoantibody markers of neural degeneration are associated with post-mortem histopathological alterations of a neurologically injured pilot. *Journal of biological physics and chemistry 14, 34-53*

Case report

- Autopsy: Histopathological examination
- Relatively high amount of lymphocytes in the myocardium
- Thickening of the arterial walls with lymphocytic infiltration
- Lymphocytes in excessive amount in tissues of the mediastinum
- Endoneural T-lymphocyte invasion and gross axonal demyelination in peripheral nerves
- Demyelination, cell loss, apoptosis and spongiosis in central nervous system

- significantly higher levels of auto-antibodies

Abou-Donia, M. B., Goot, F. R. W. van der, Mulder, M. F. A. (2014) Autoantibody markers of neural degeneration are associated with post-mortem histopathological alterations of a neurologically injured pilot. *Journal of biological physics and chemistry 14, 34-53*

Materials

- Formalin fixed paraffin embedded tissue samples
- 4 male pilots
- Aerotoxic syndrome ascribed symptoms
- Cardiac tissue
- Nervous tissue
- Other organ tissue

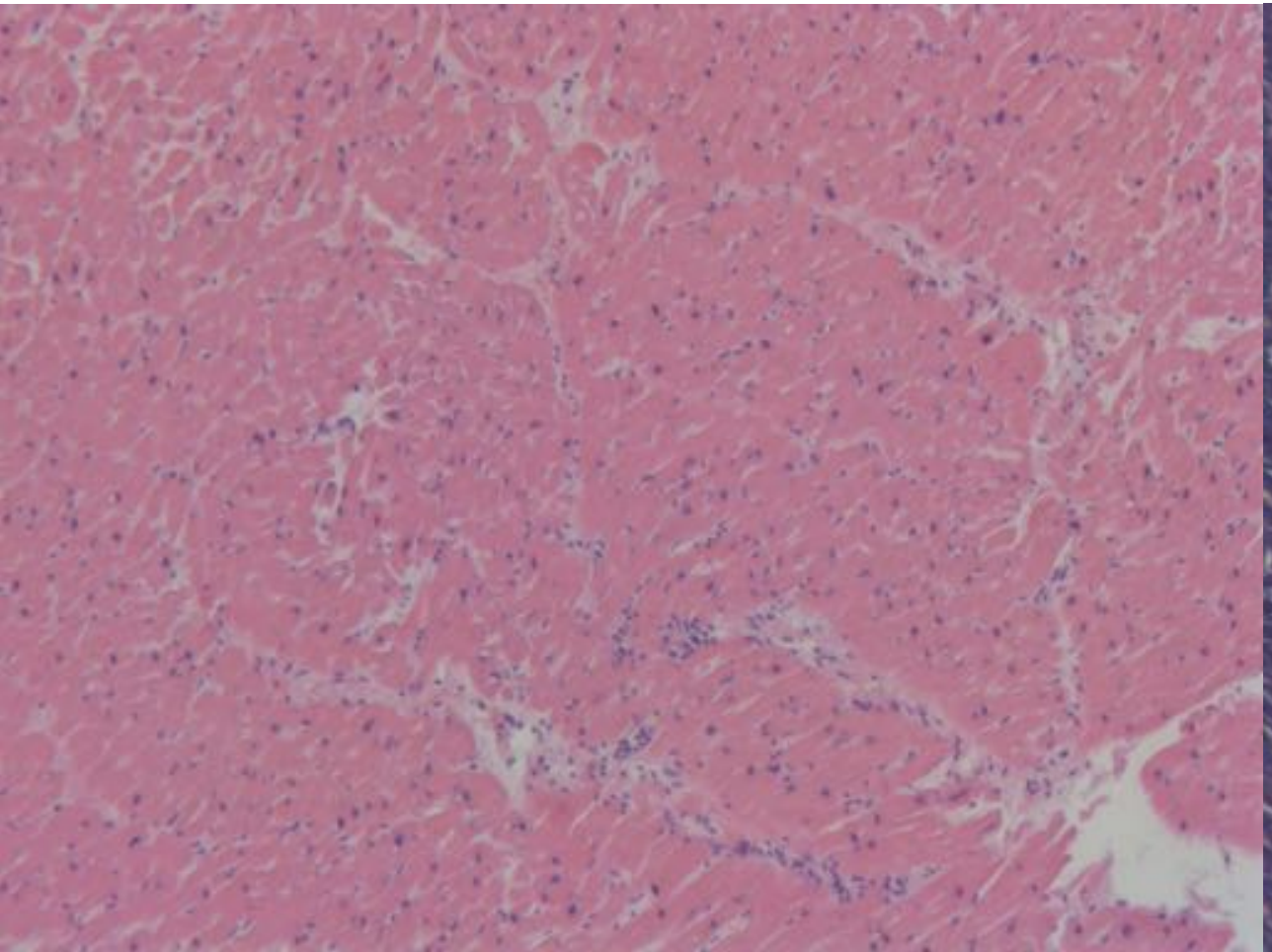
Methods

- 5 um thick tissue sections
- Hematoxylin/Eosin (HE) Phosphotungstic acid-haematoxylin (PTAH) and Klüver-PAS according to standard methods.
- Immunohistochemical staining for CD-45, CD-3, CD68, MPO, C3D, NOX2, Neurofilament

Results

S12-40031 4 myocardium

HE



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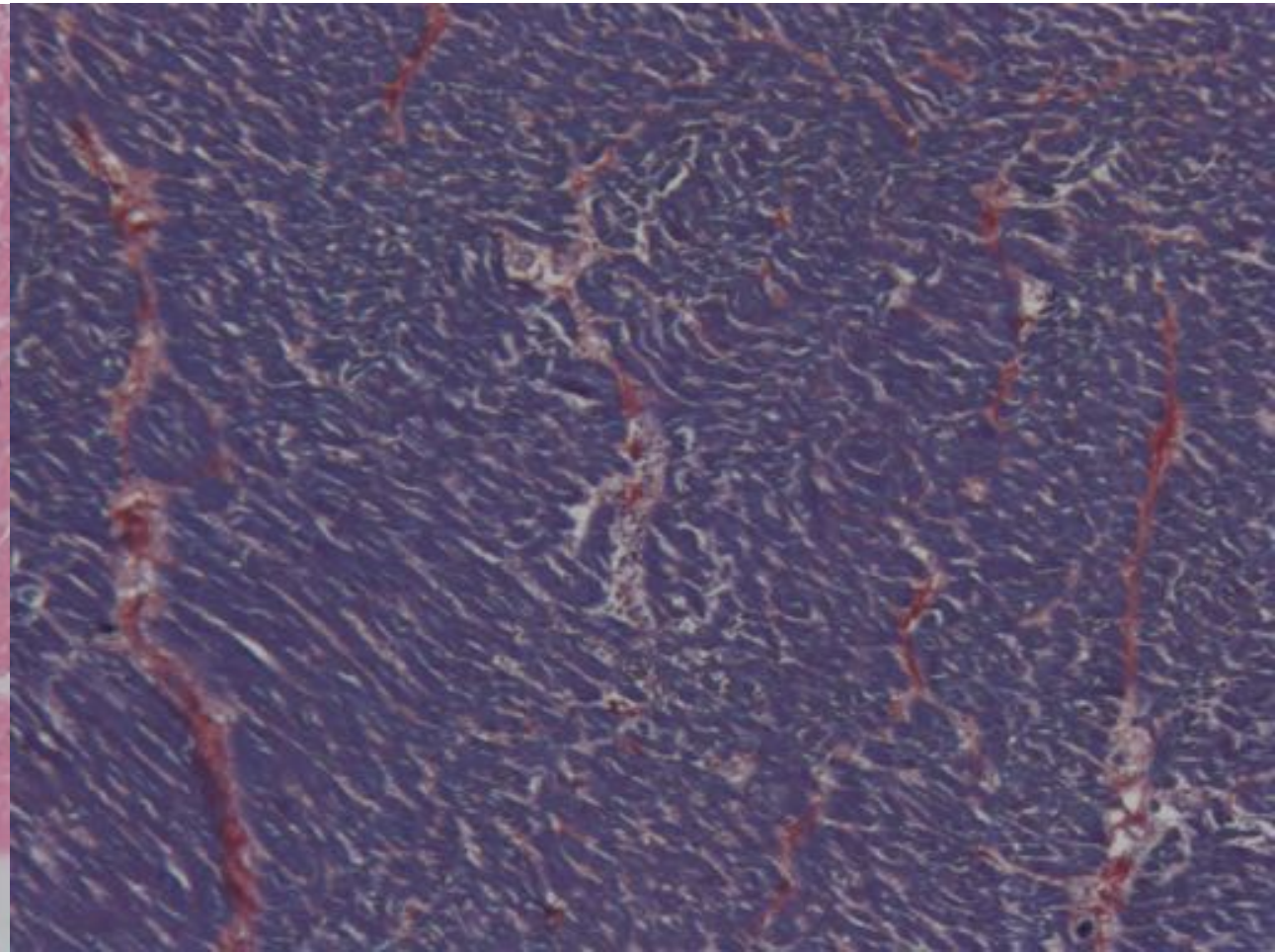
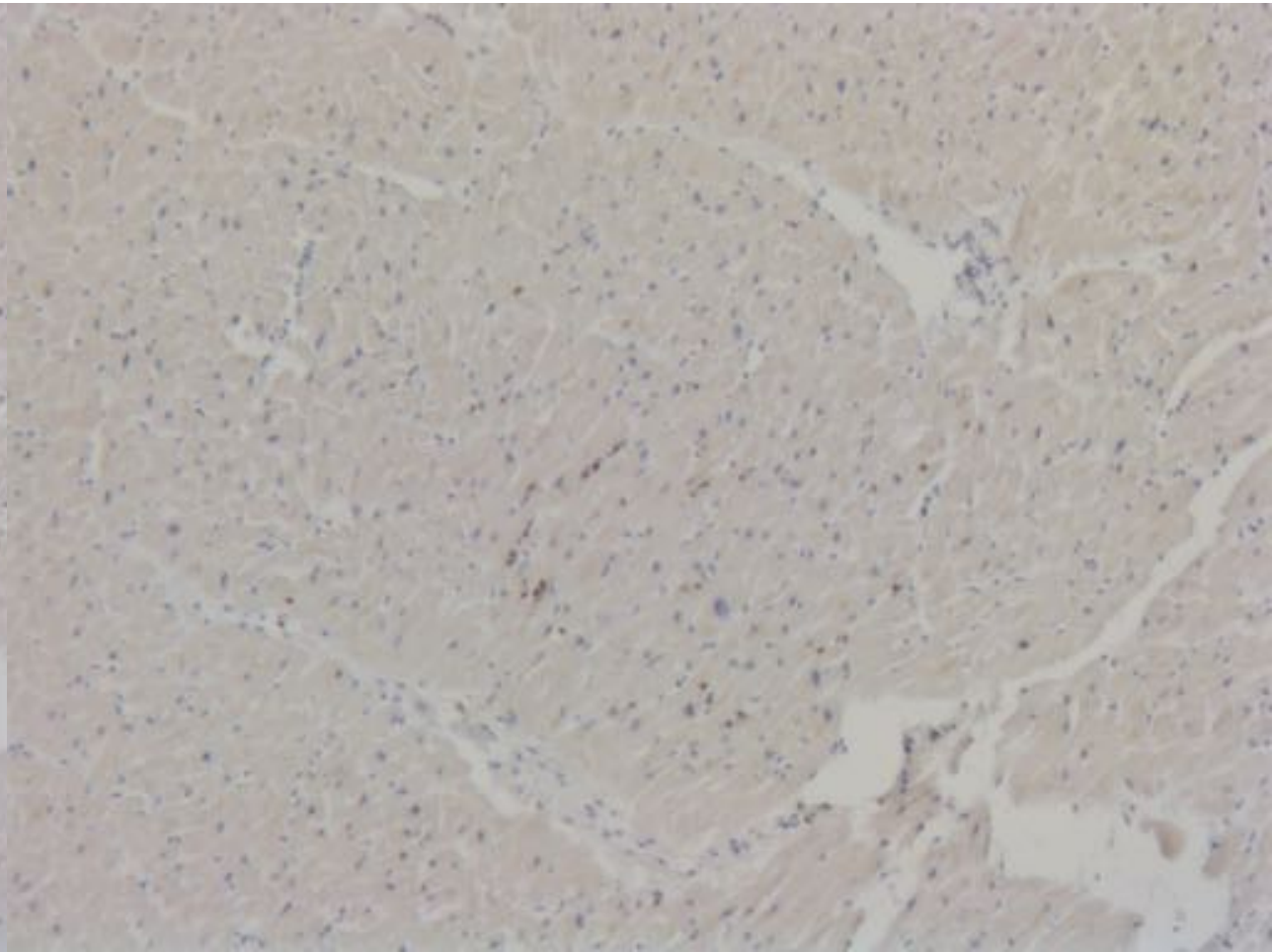


S12-40031 4 myocardium

CD45

CD3



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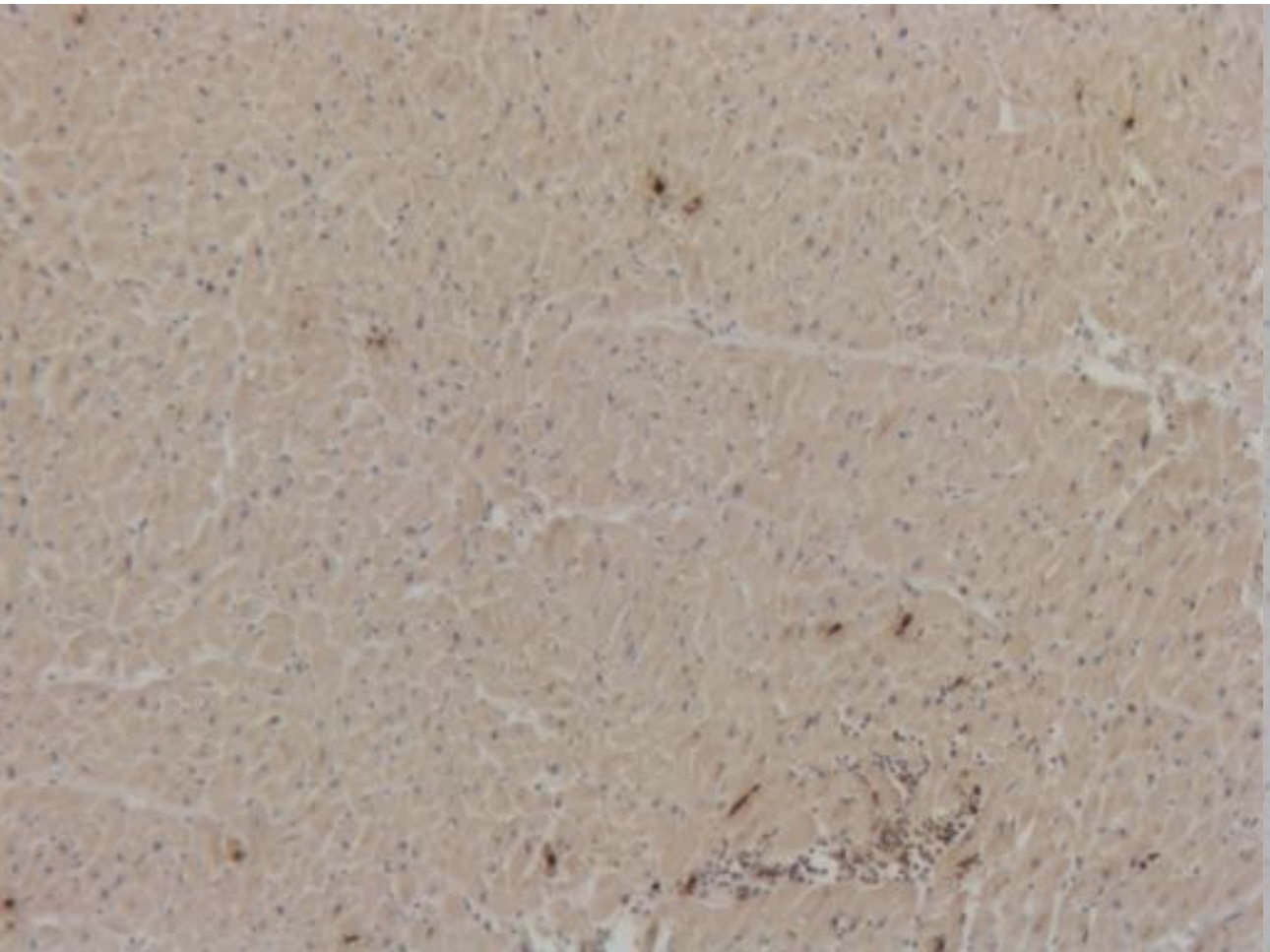
MPO



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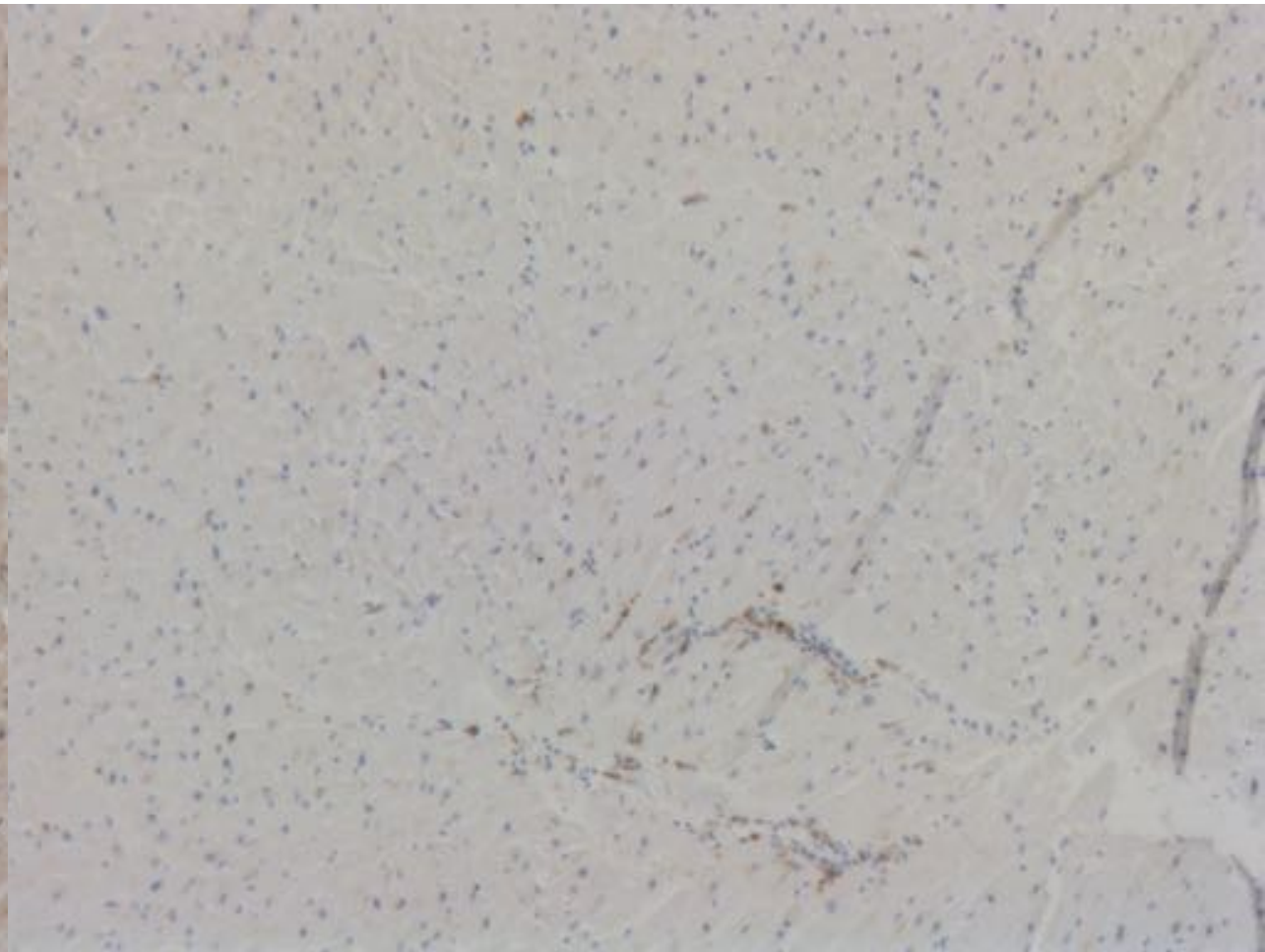

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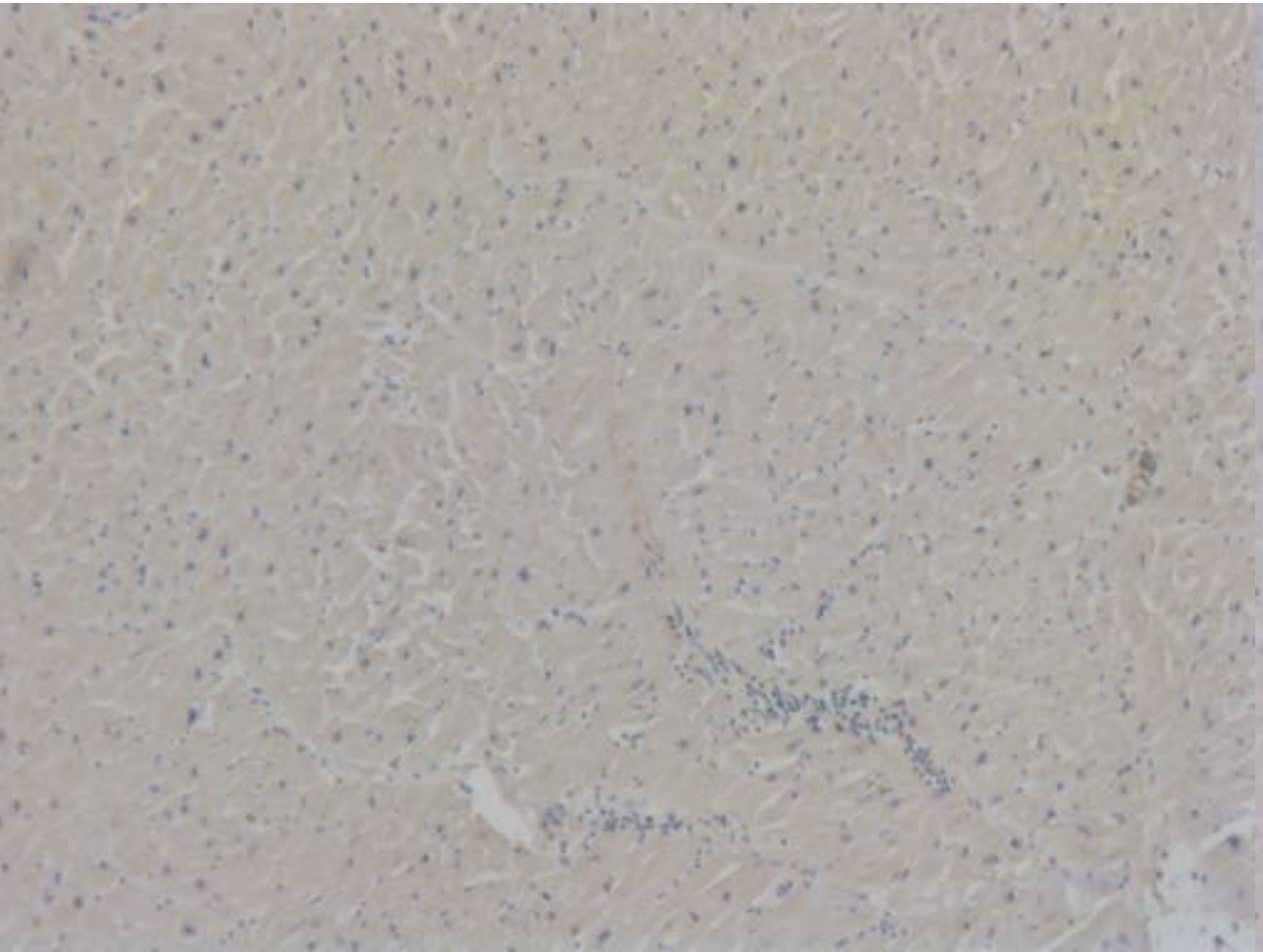
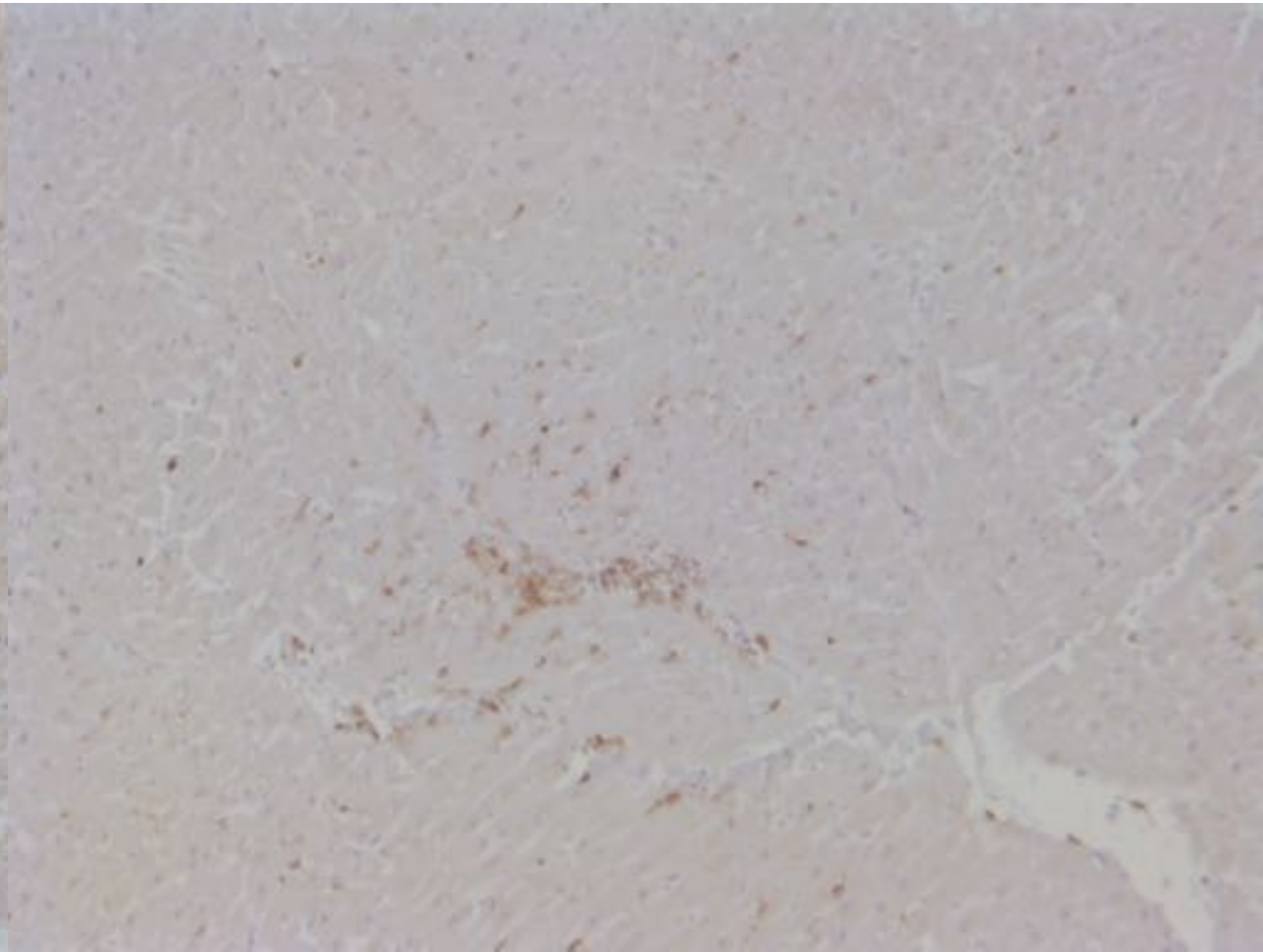
C3D

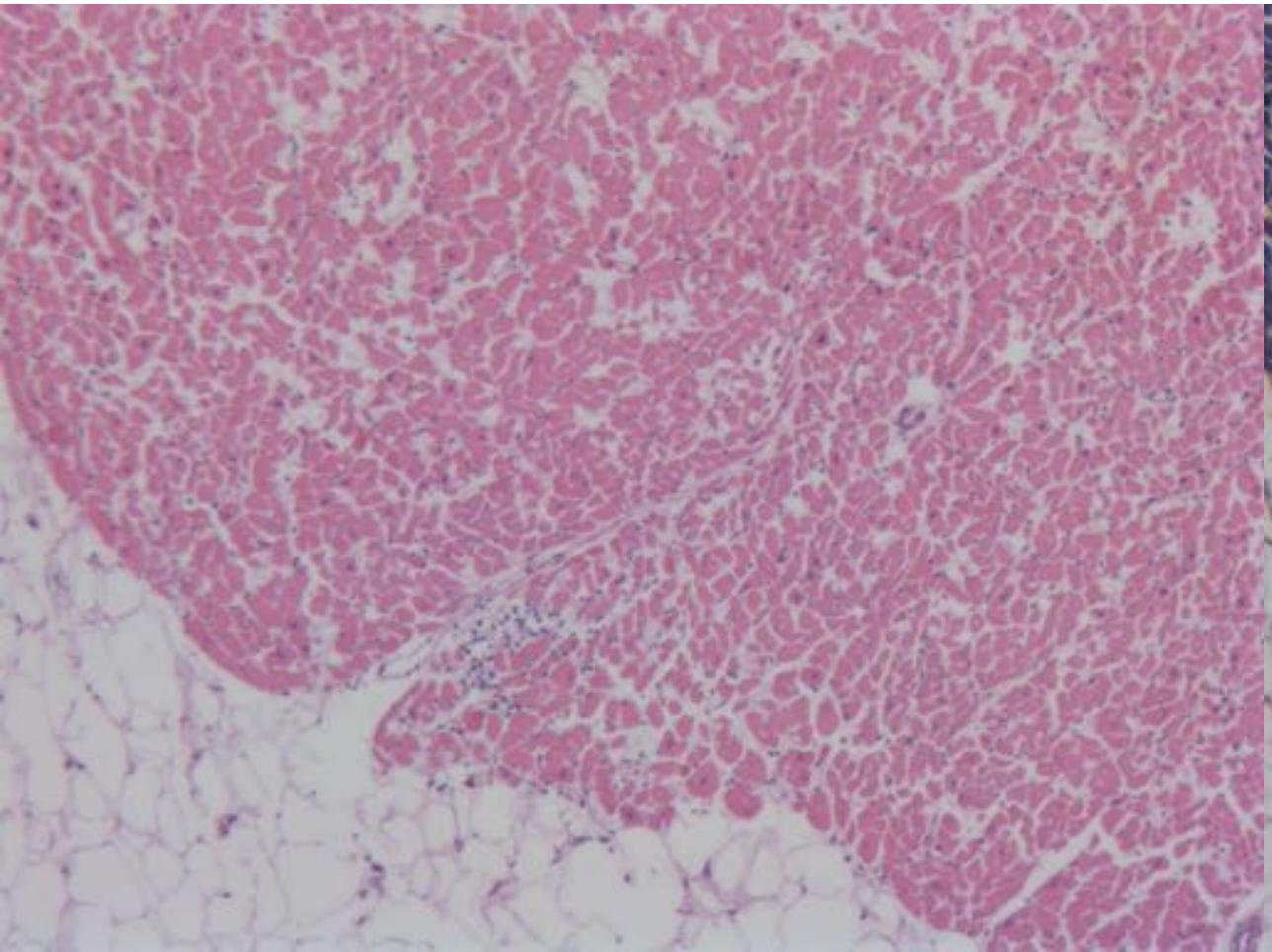


NOX2



S15-026 H hart

HE



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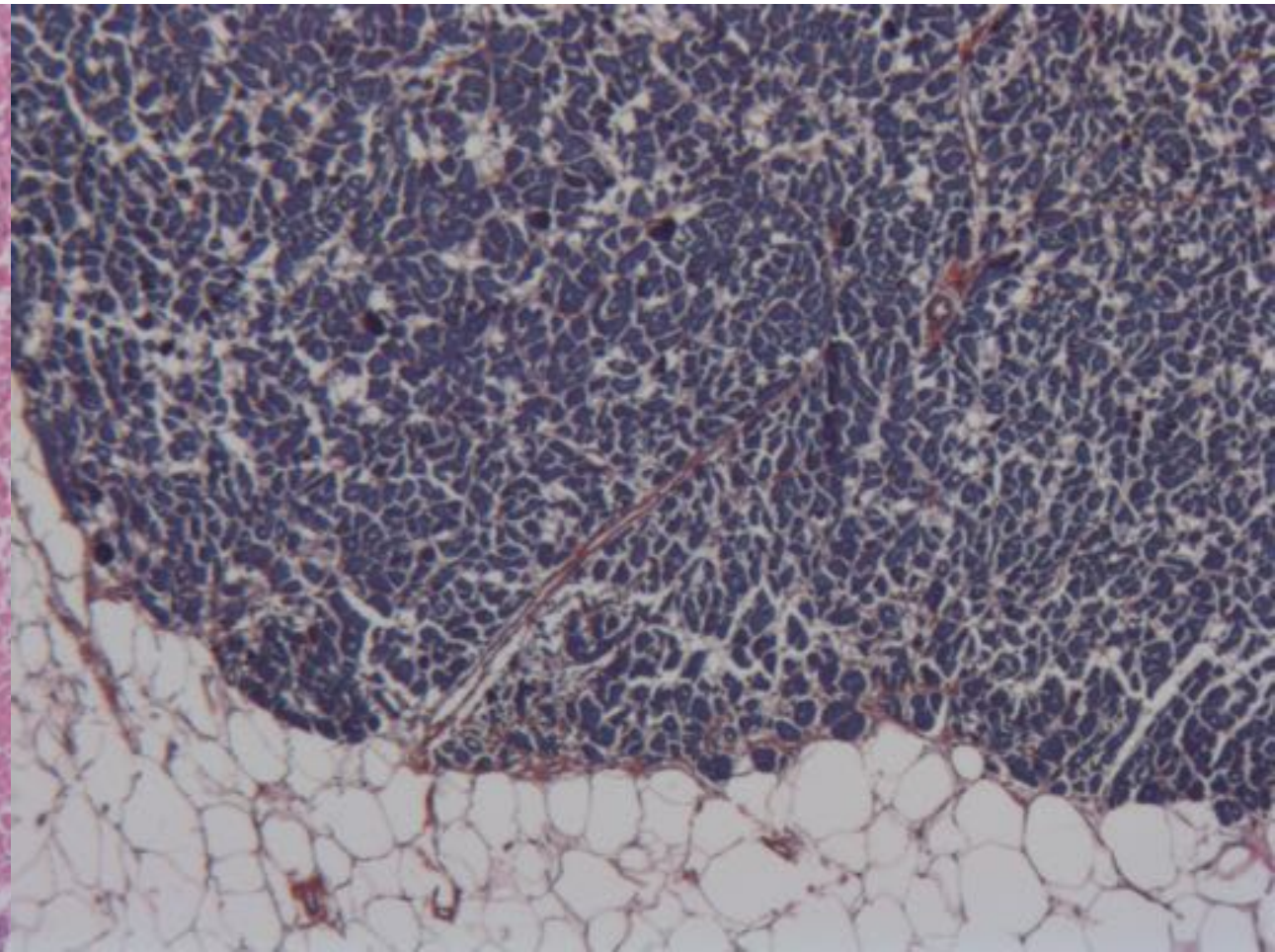

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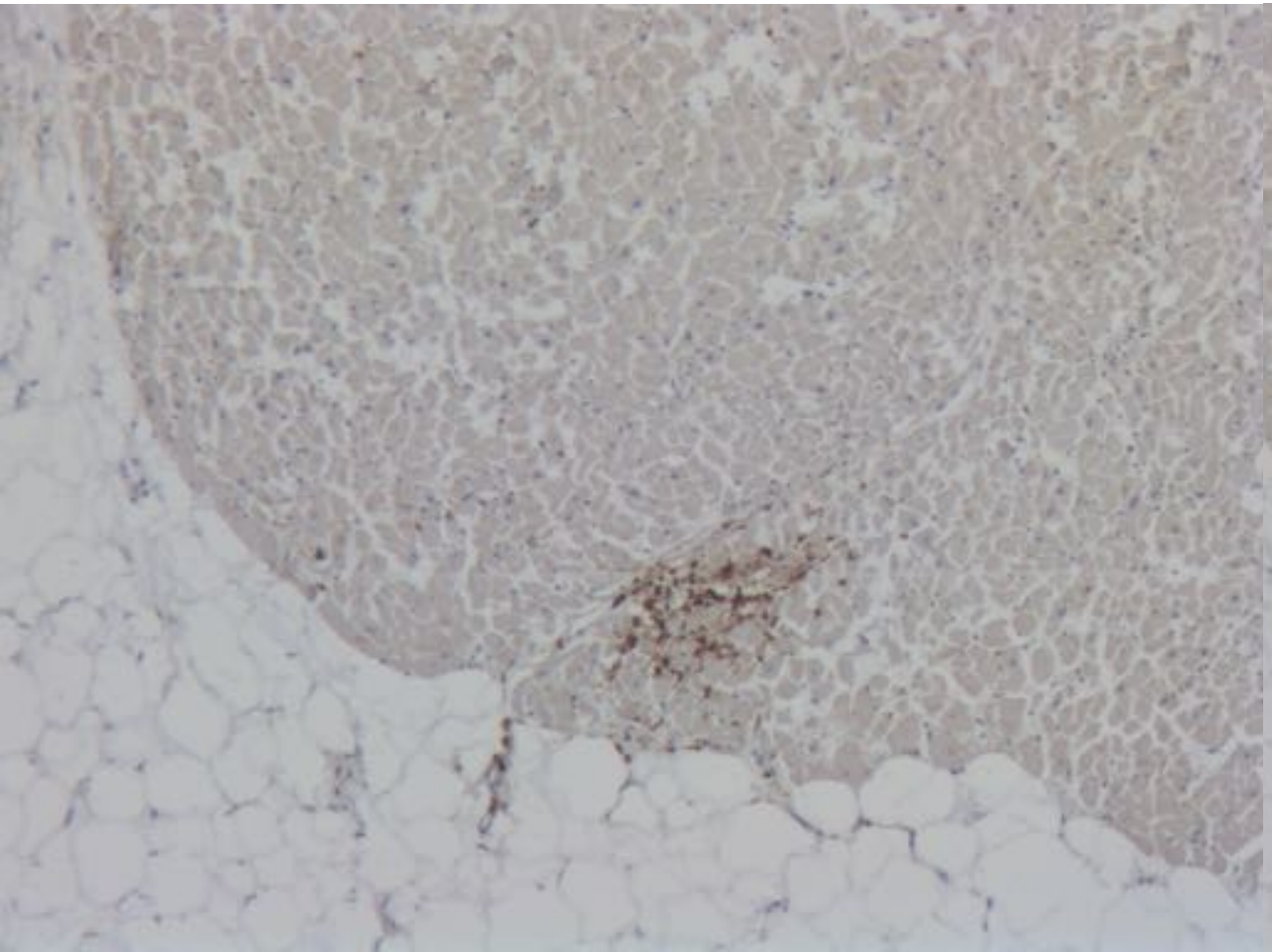

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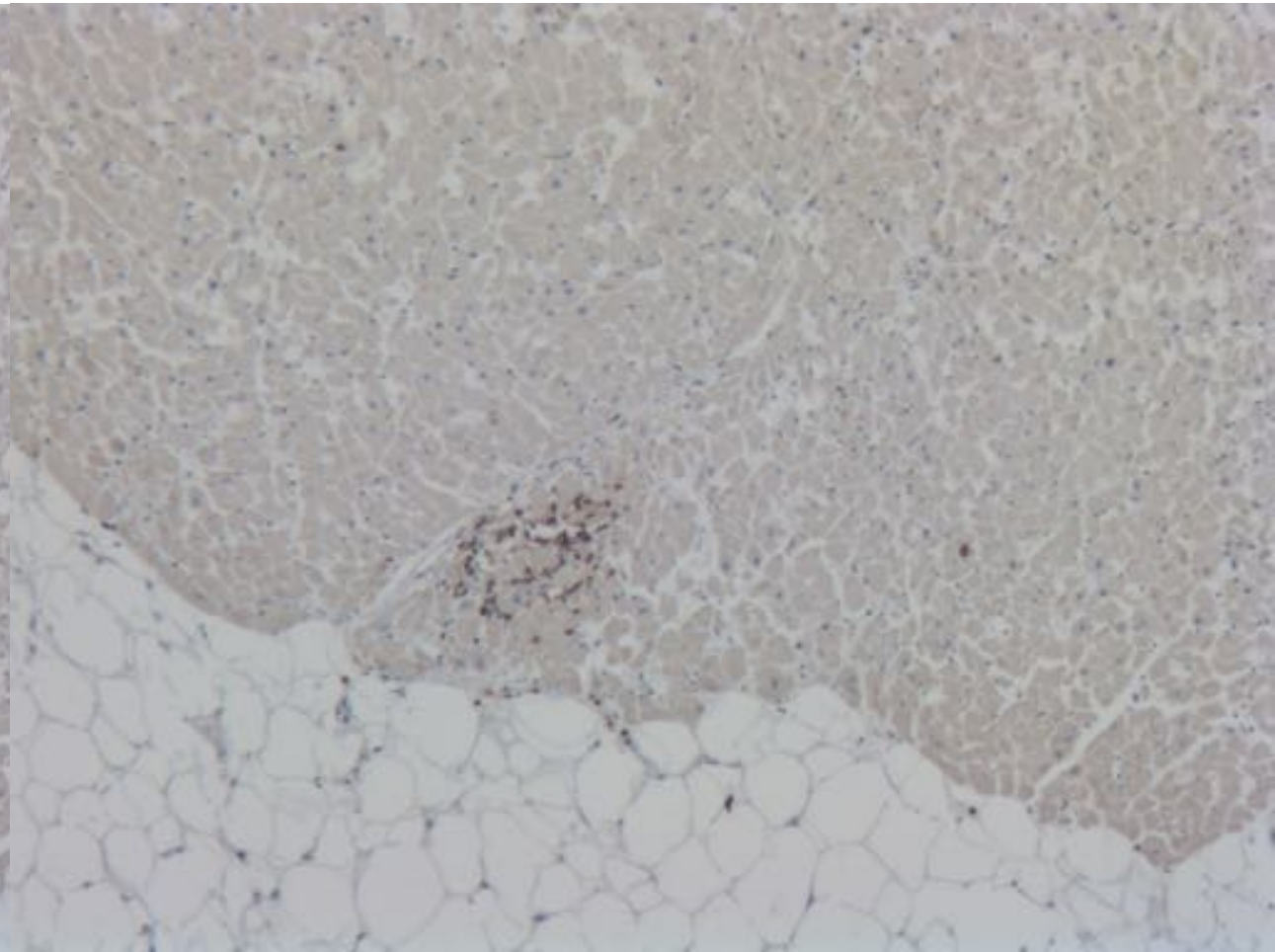

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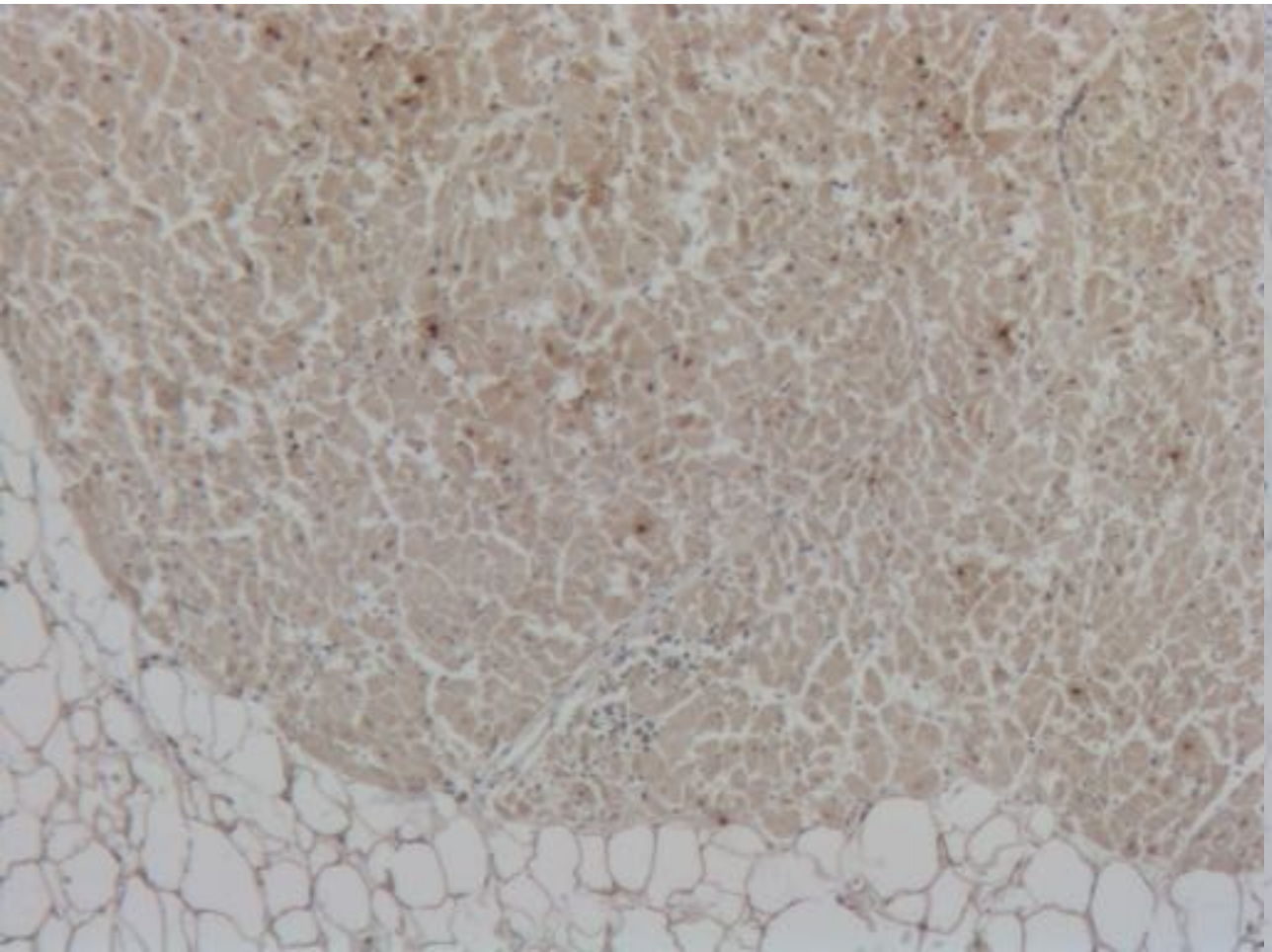

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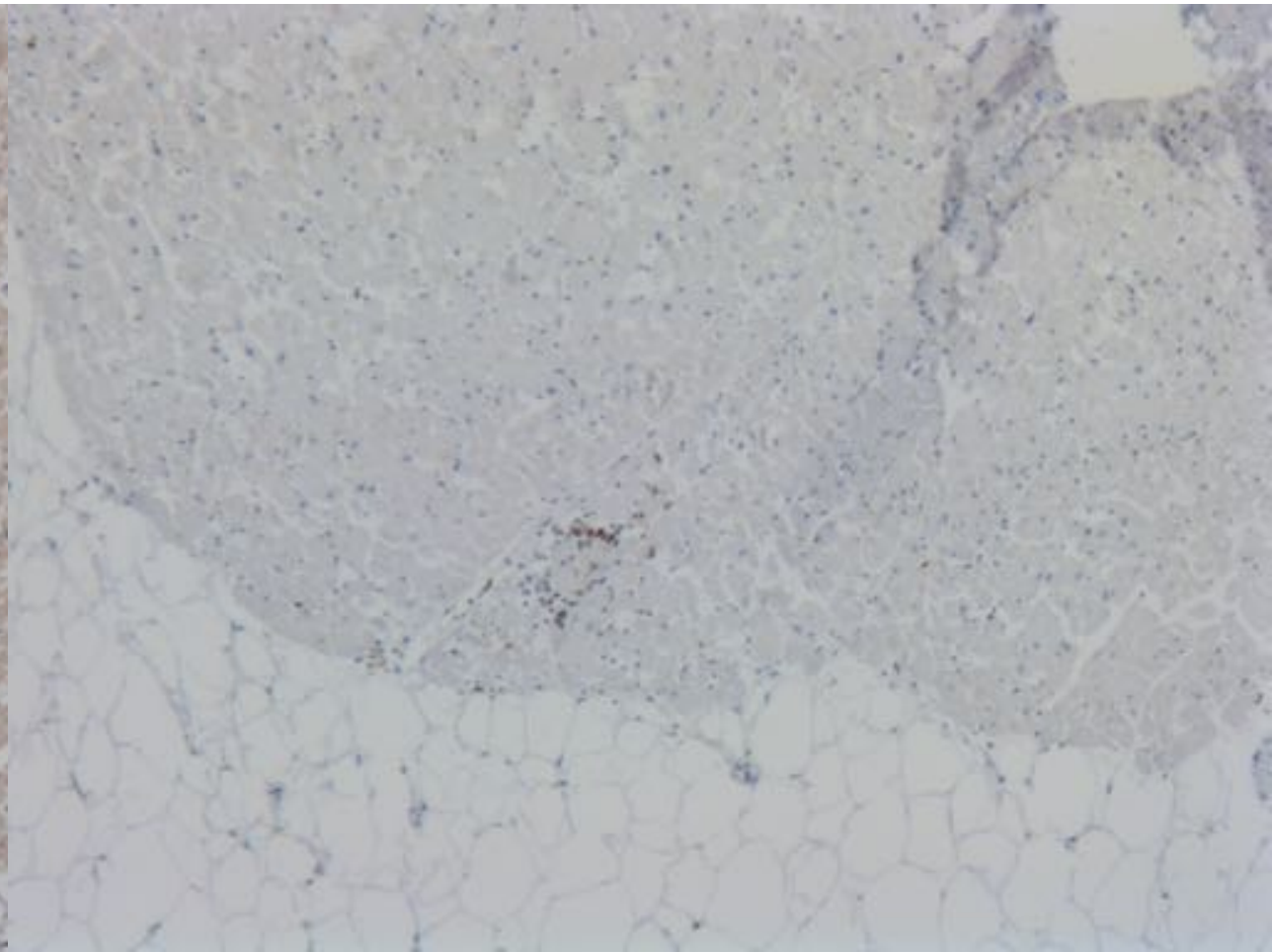

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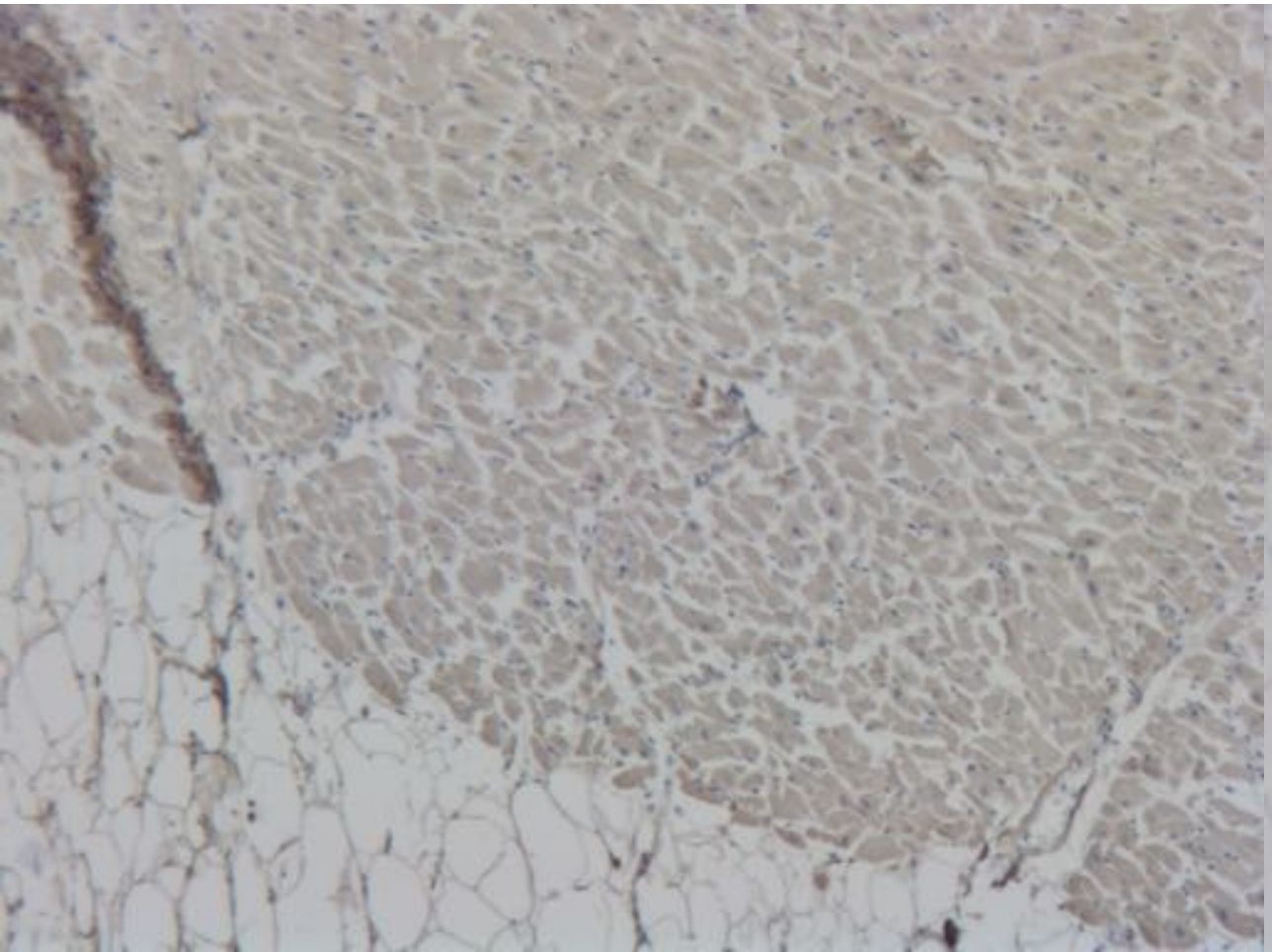
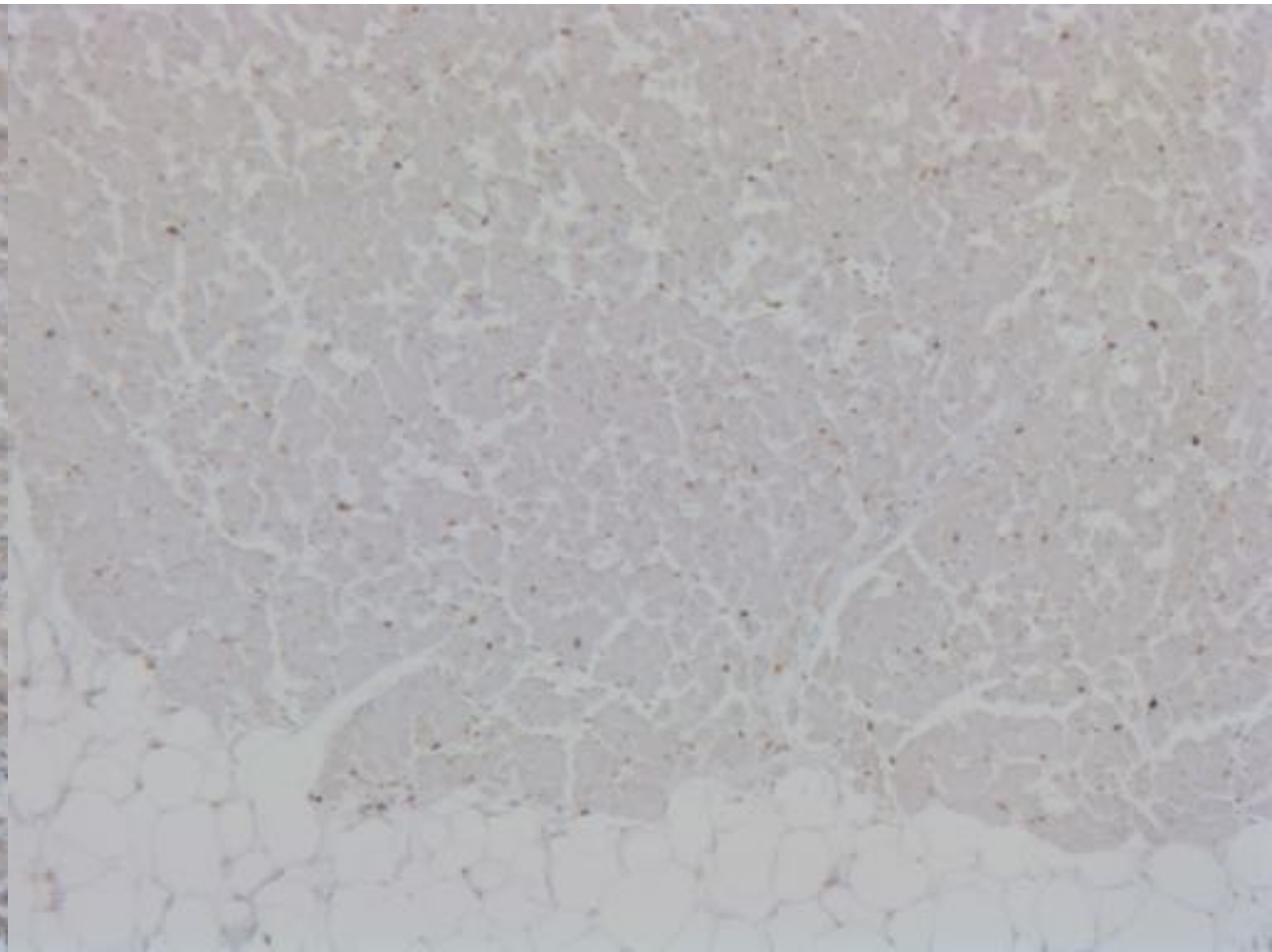
C3D

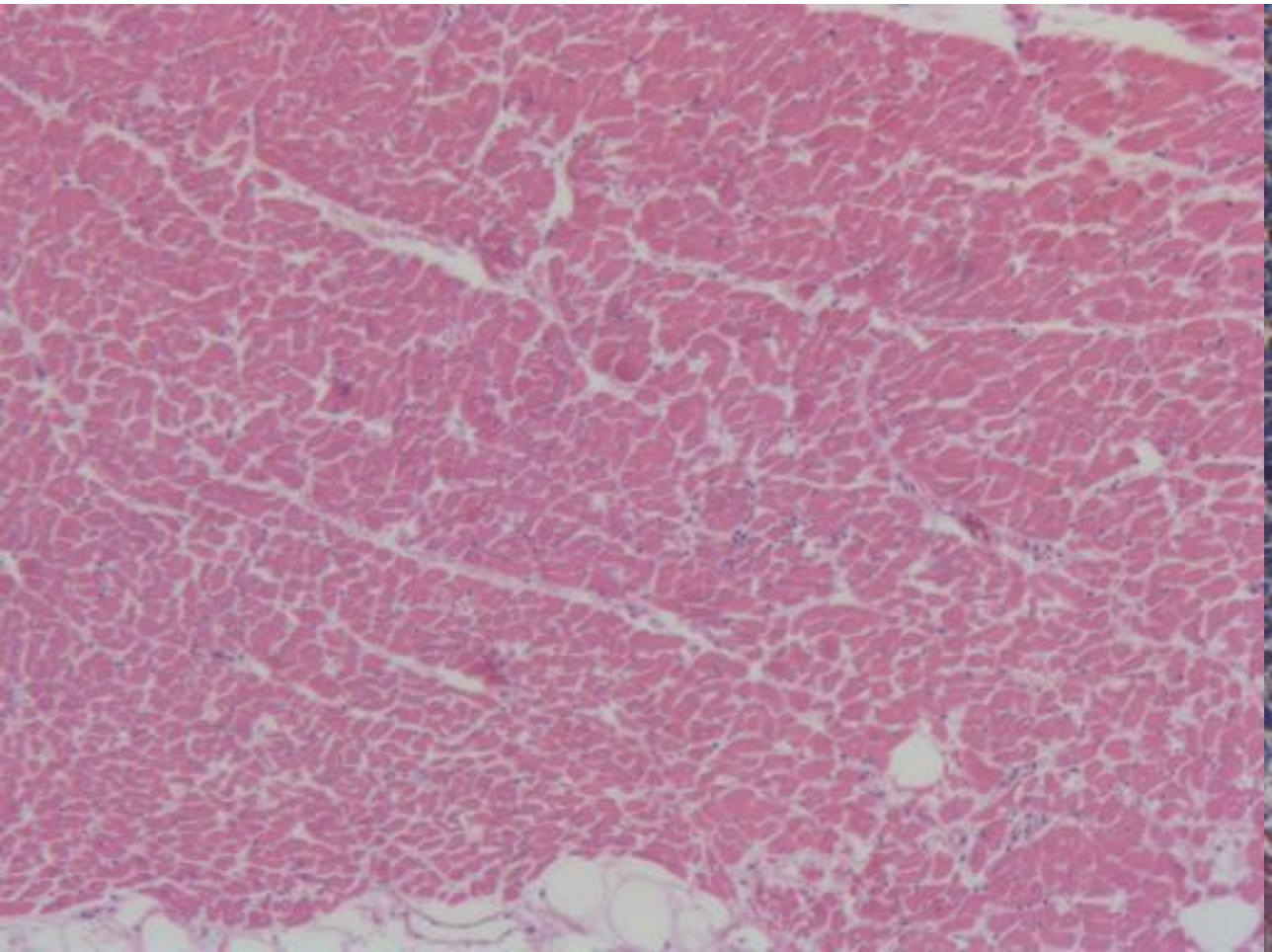


NOX2



EVU18-21085 B hart

HE



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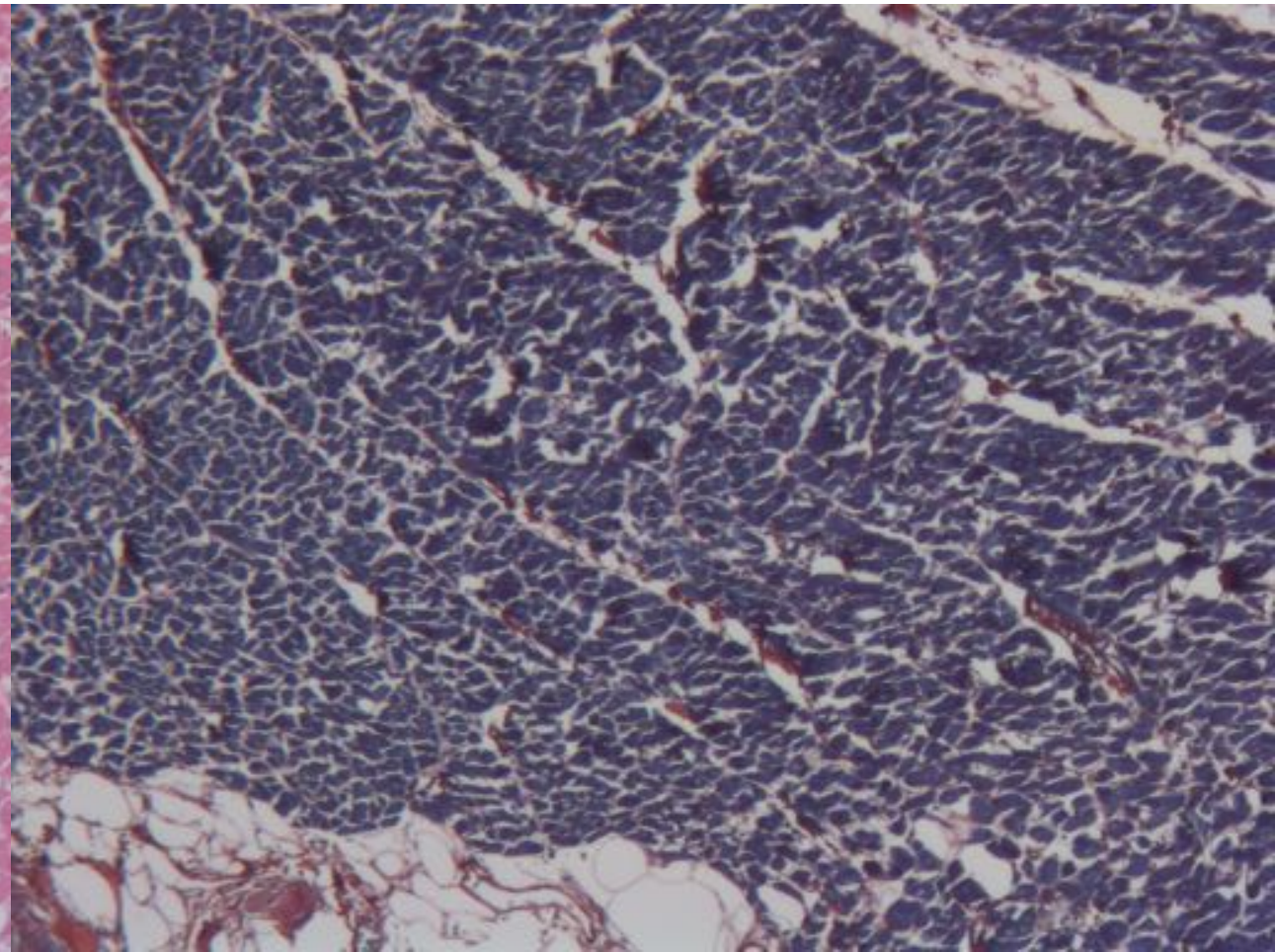
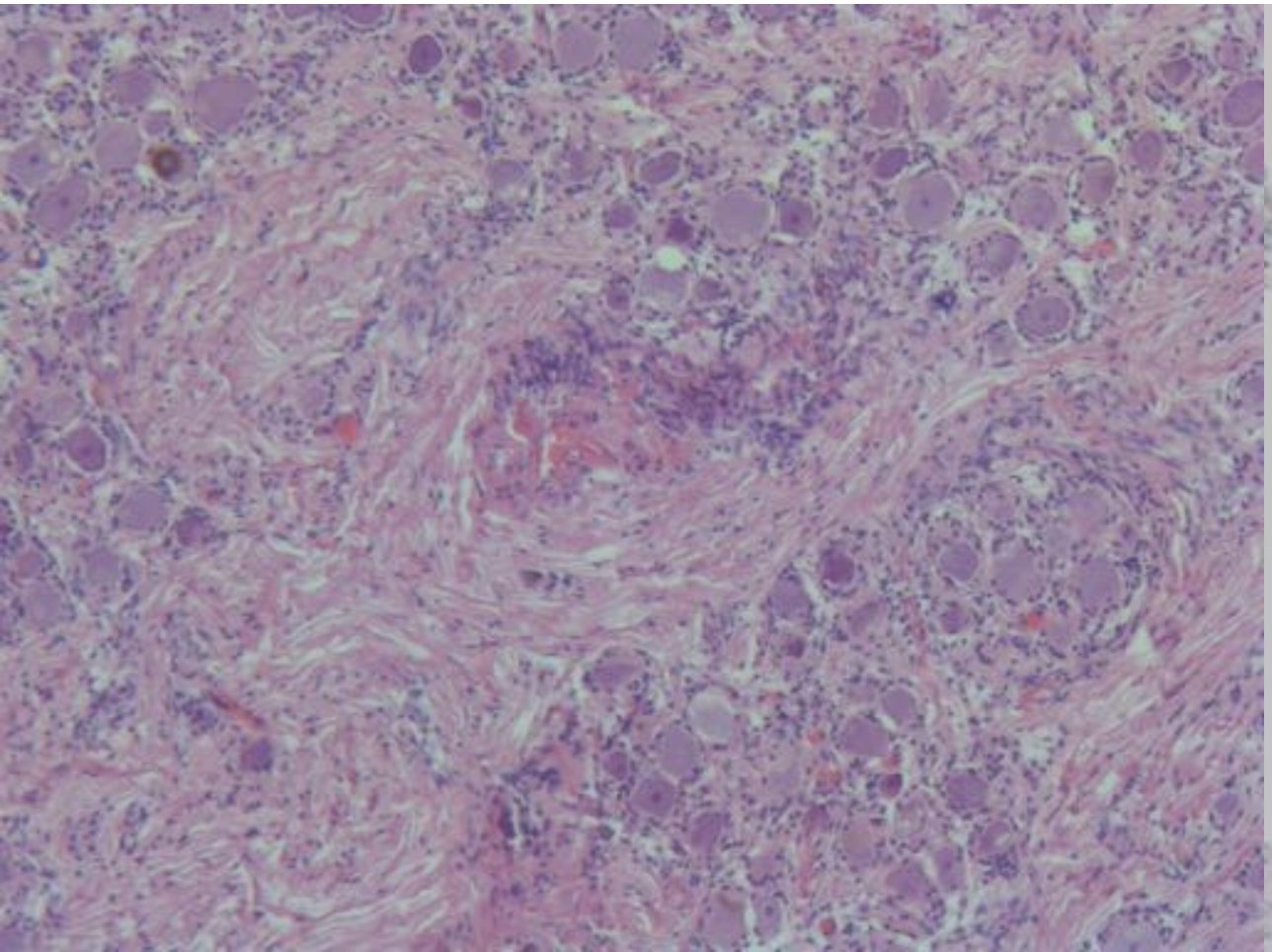


S12-40031 26 Ganglion

HE



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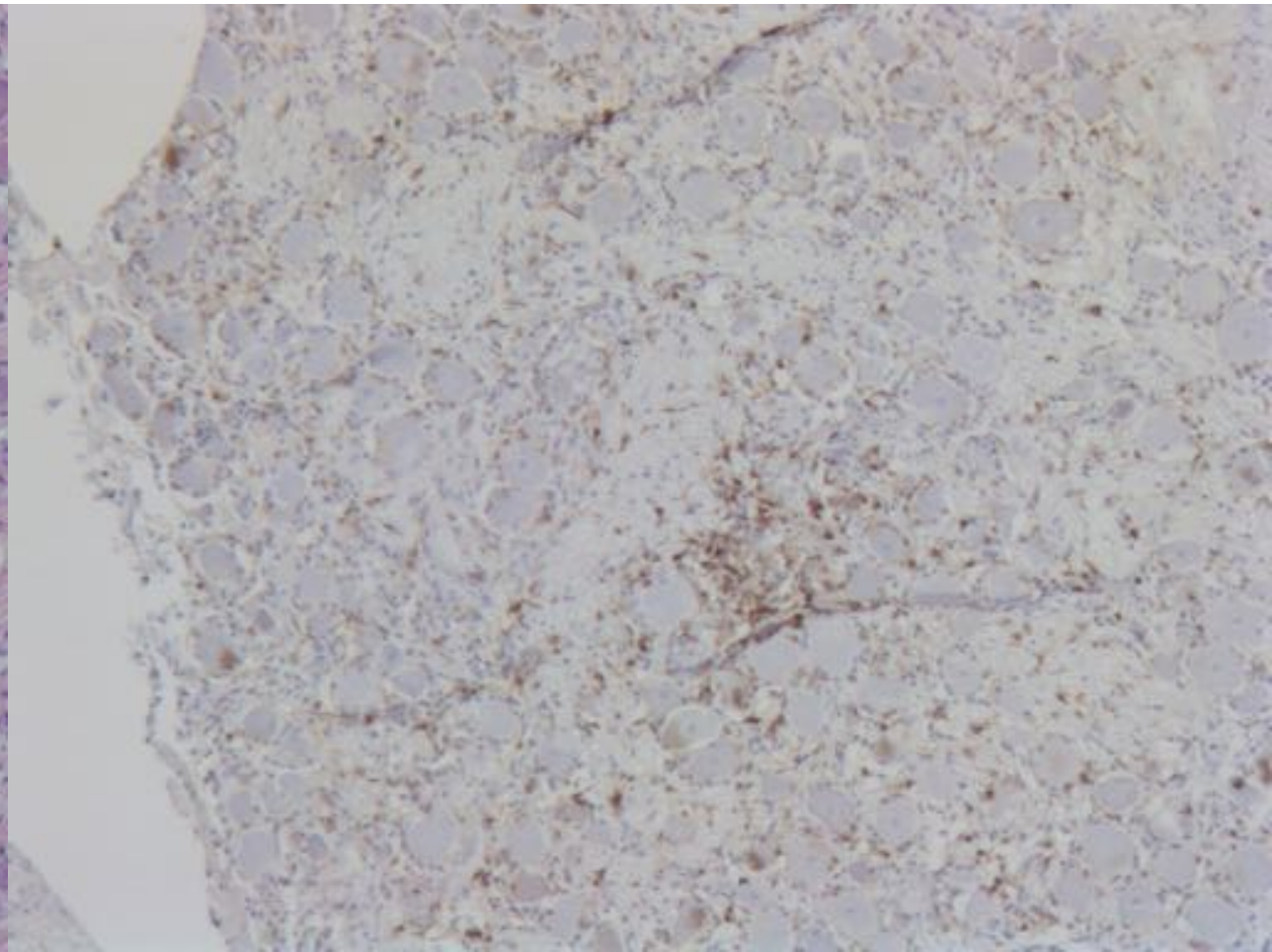

S12-40031 26 Ganglion

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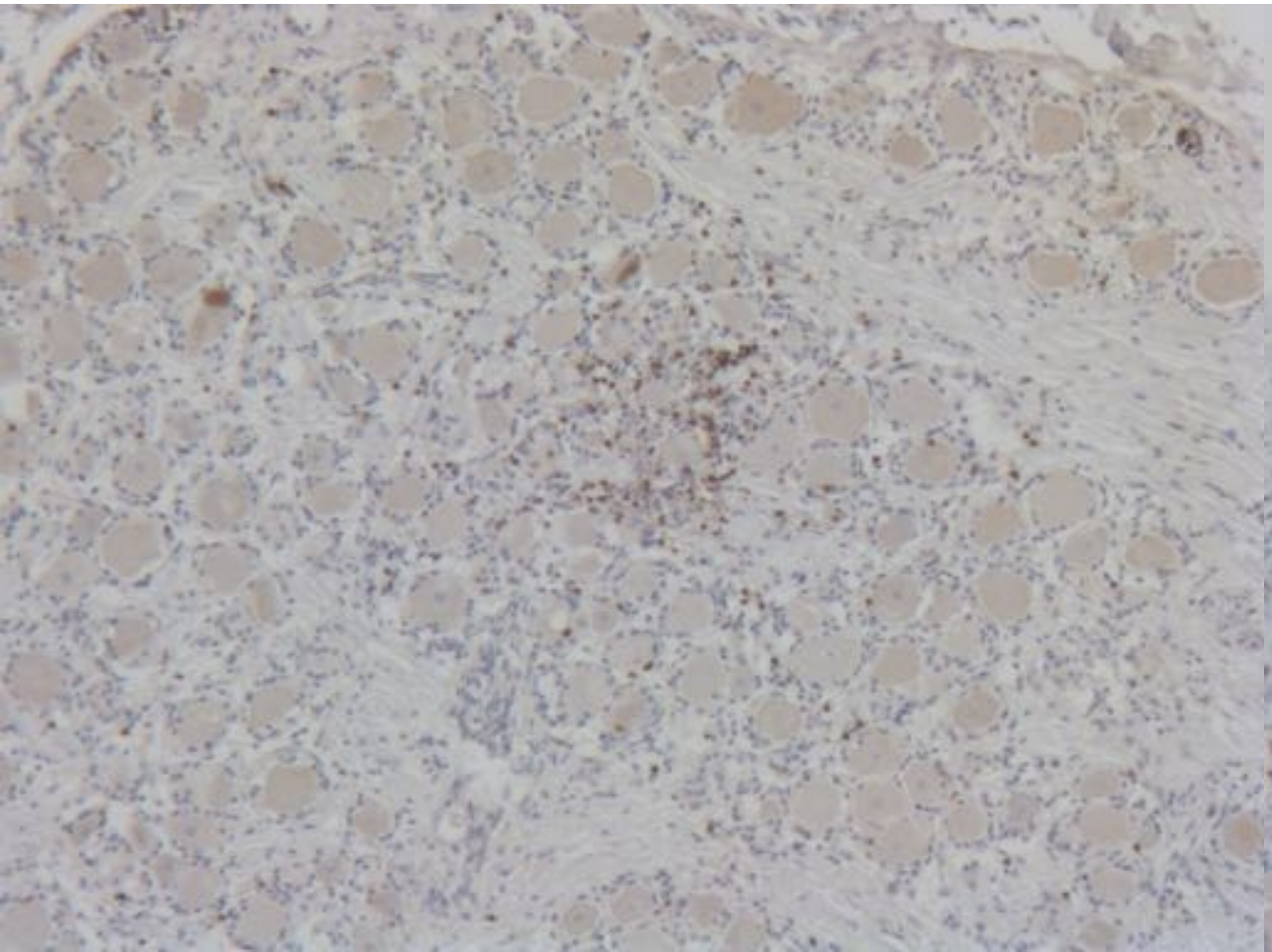

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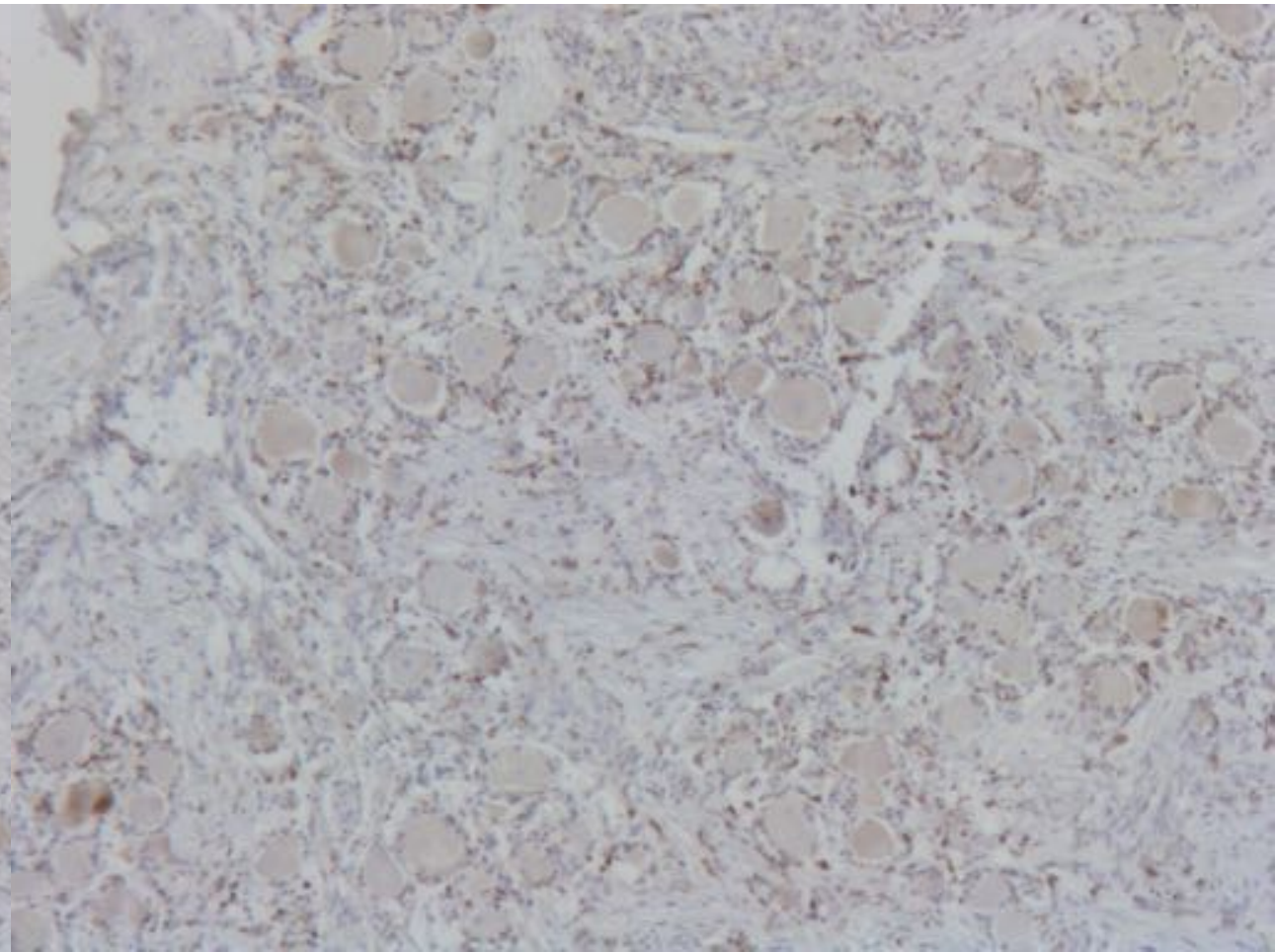
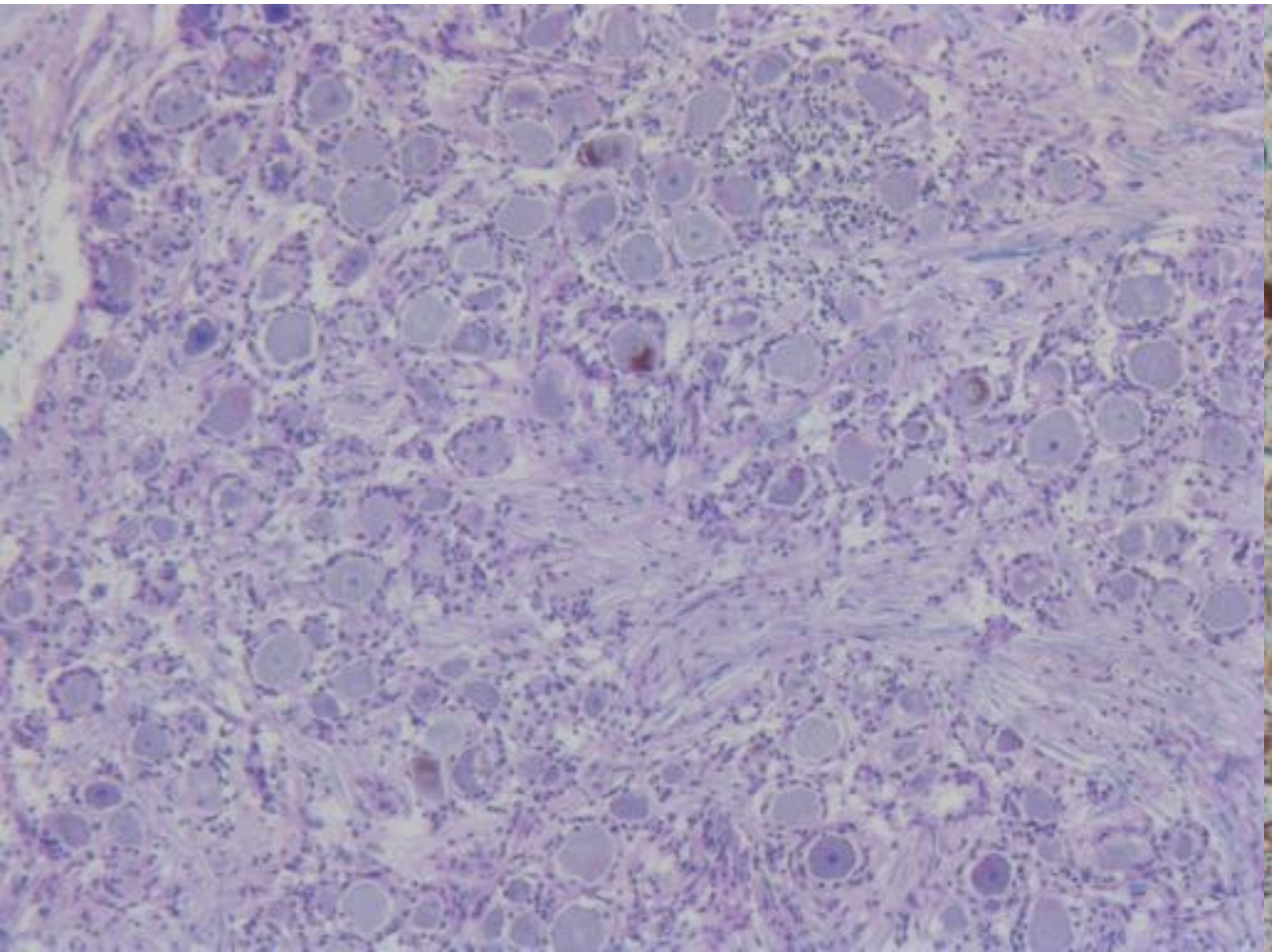


S12-40031 26 Ganglion

Kluver-PAS



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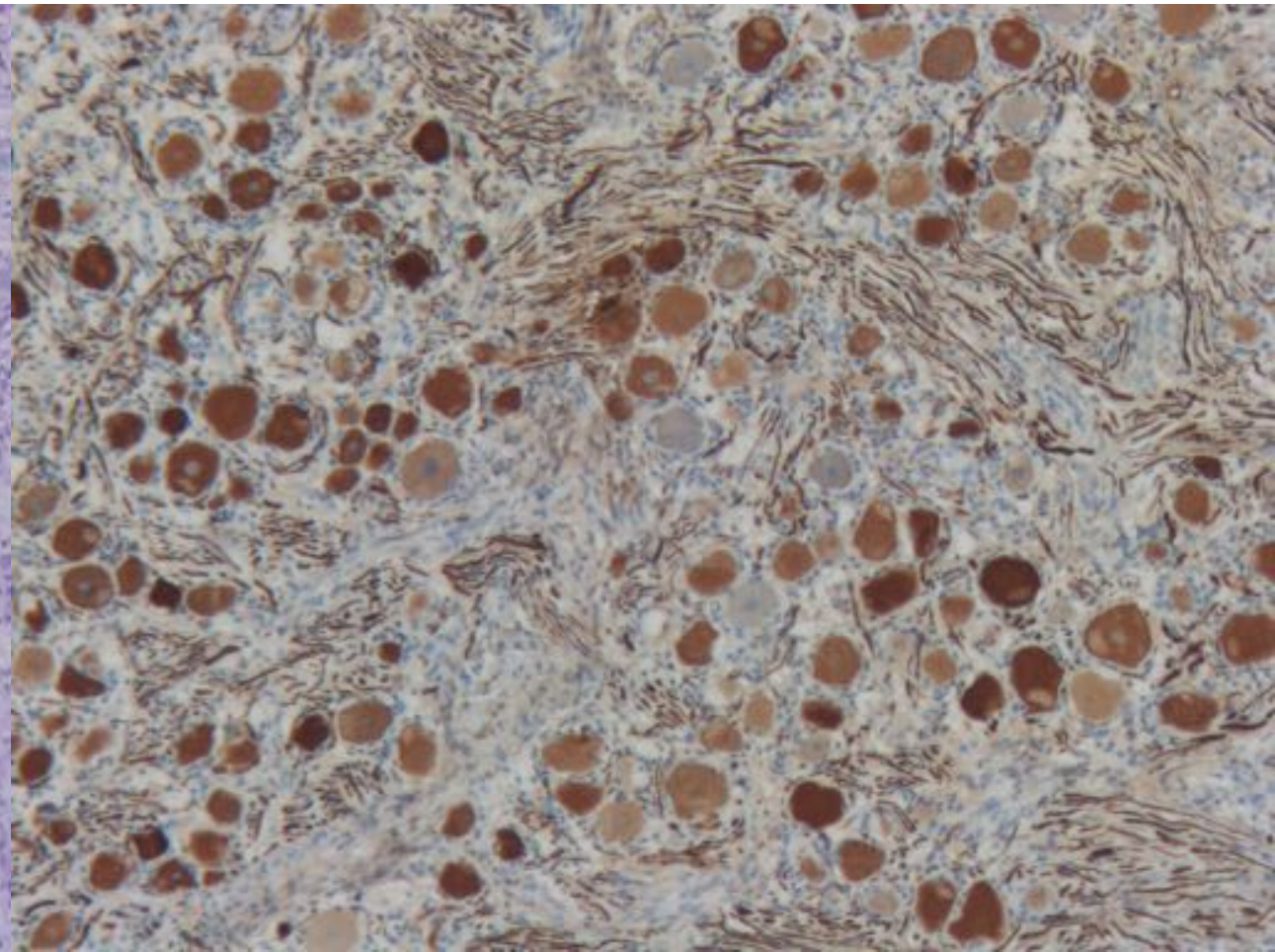

EVU18-21086 S Perifere zenuw

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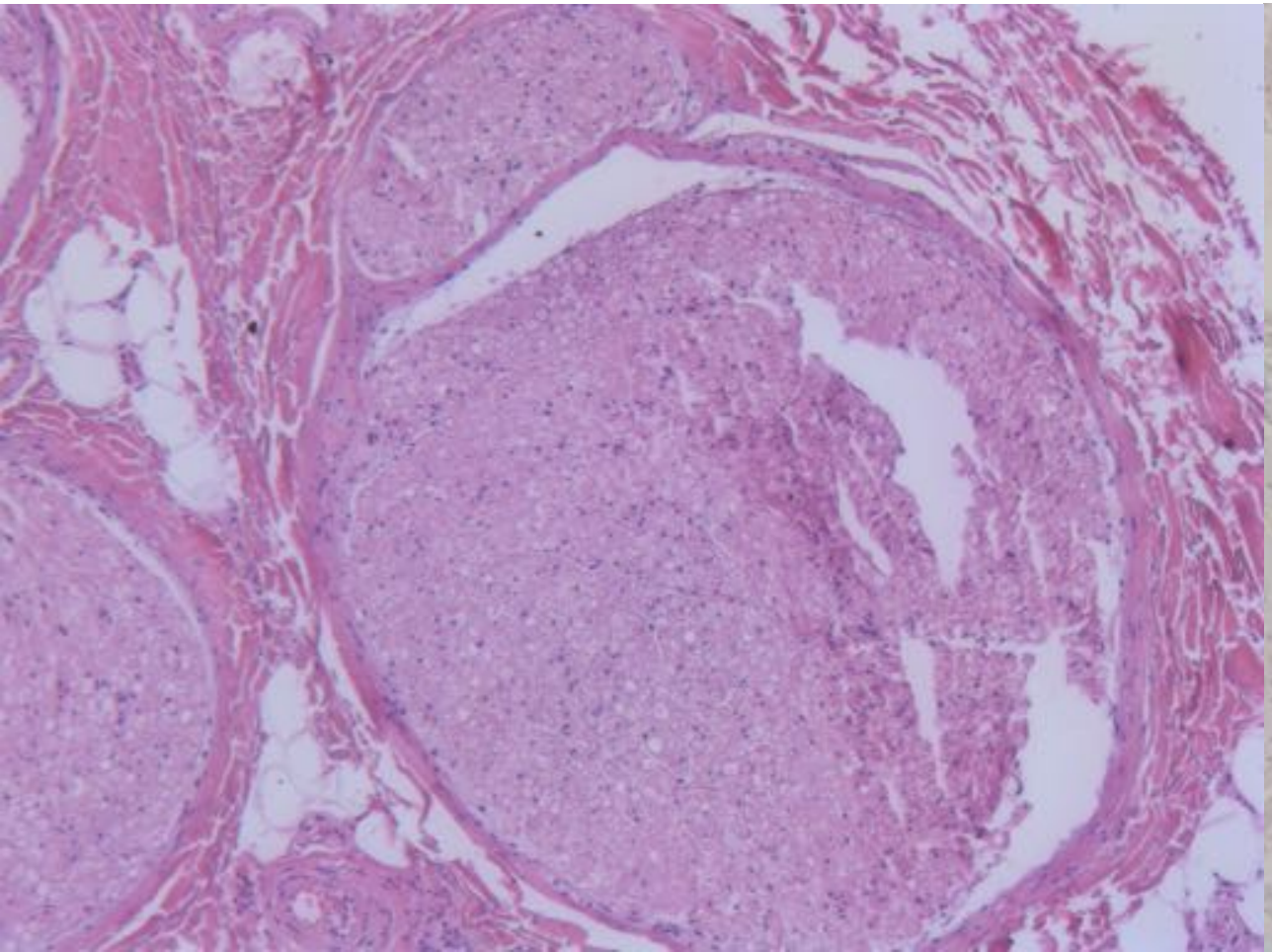

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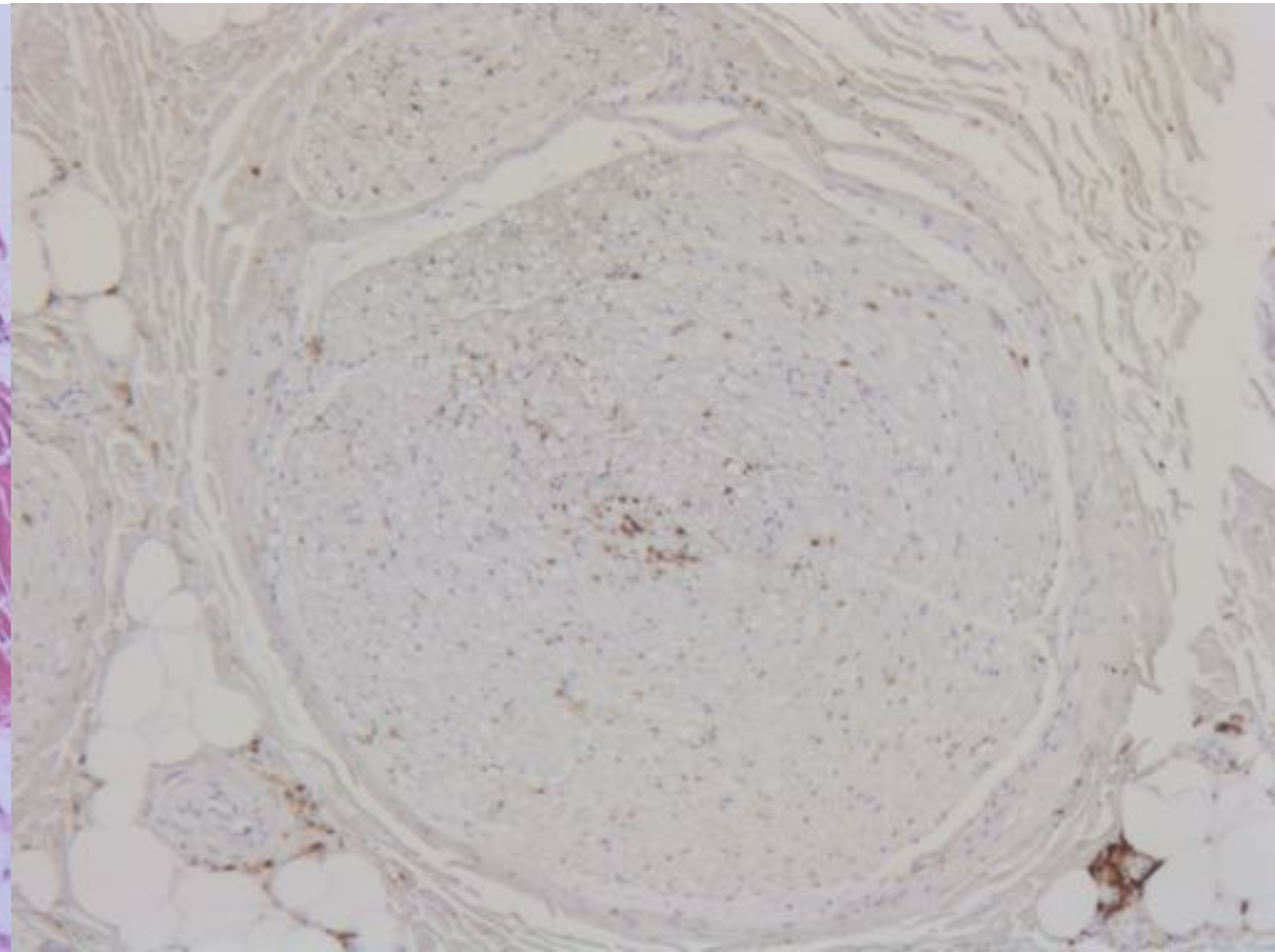

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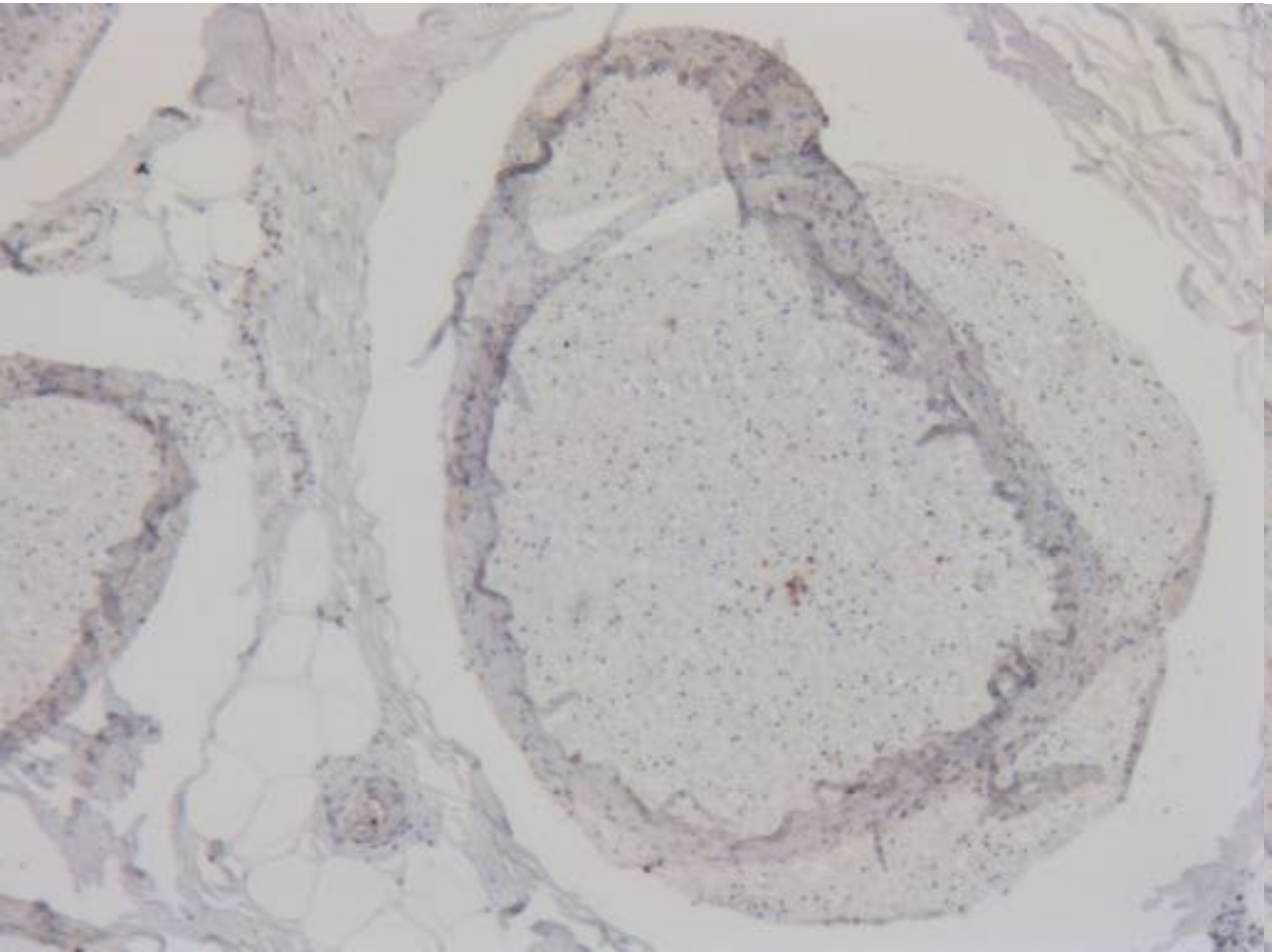

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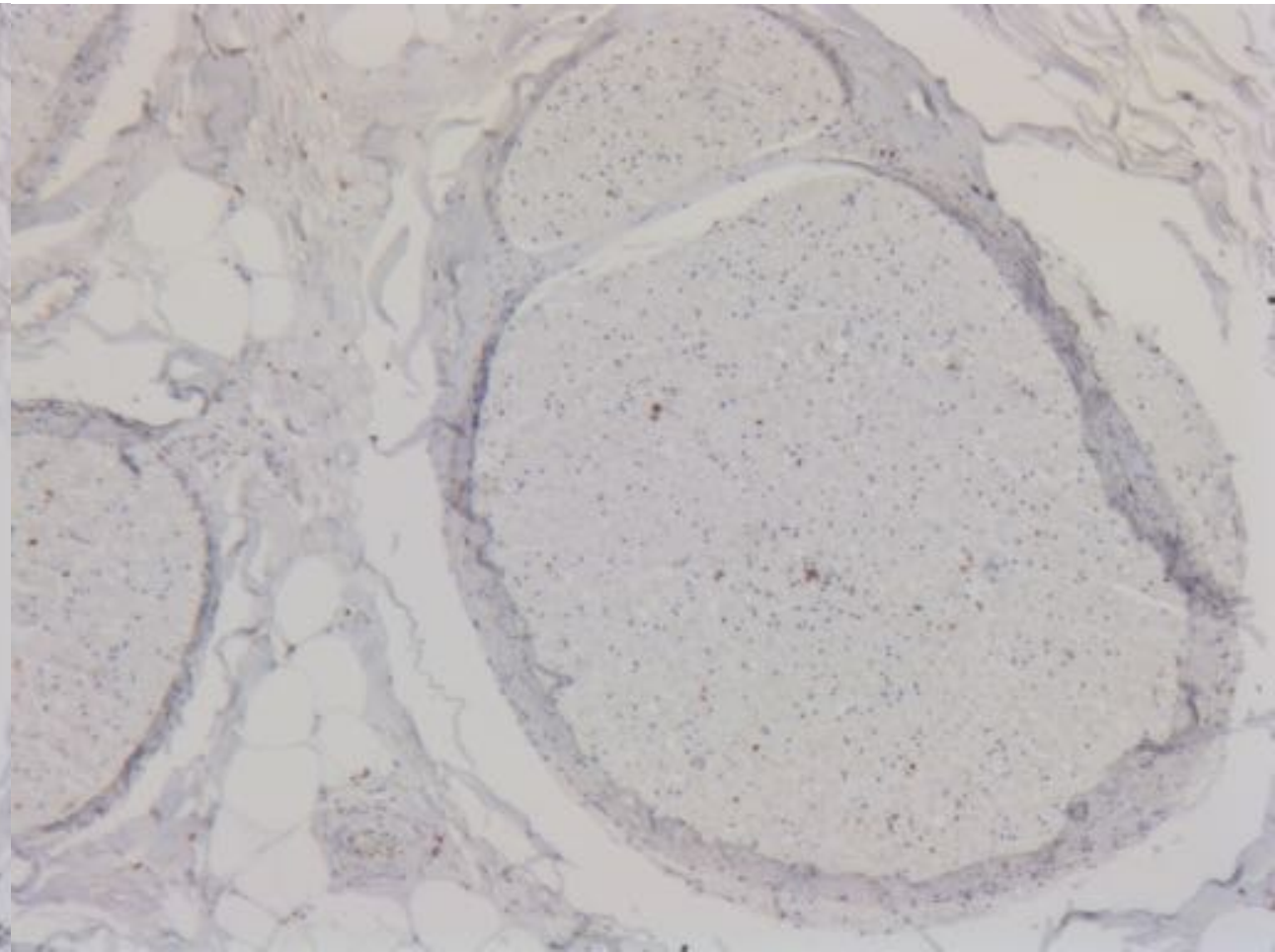

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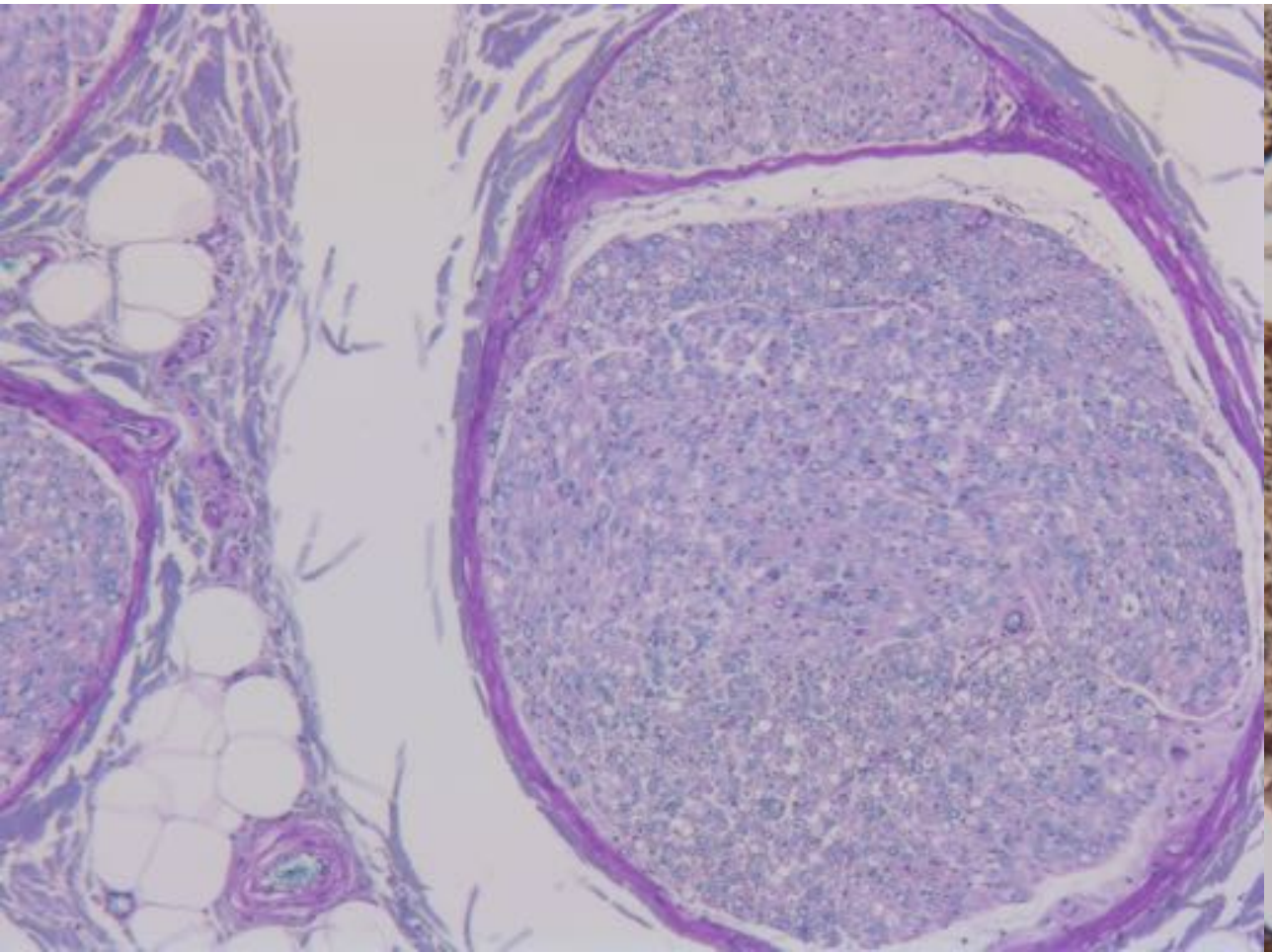

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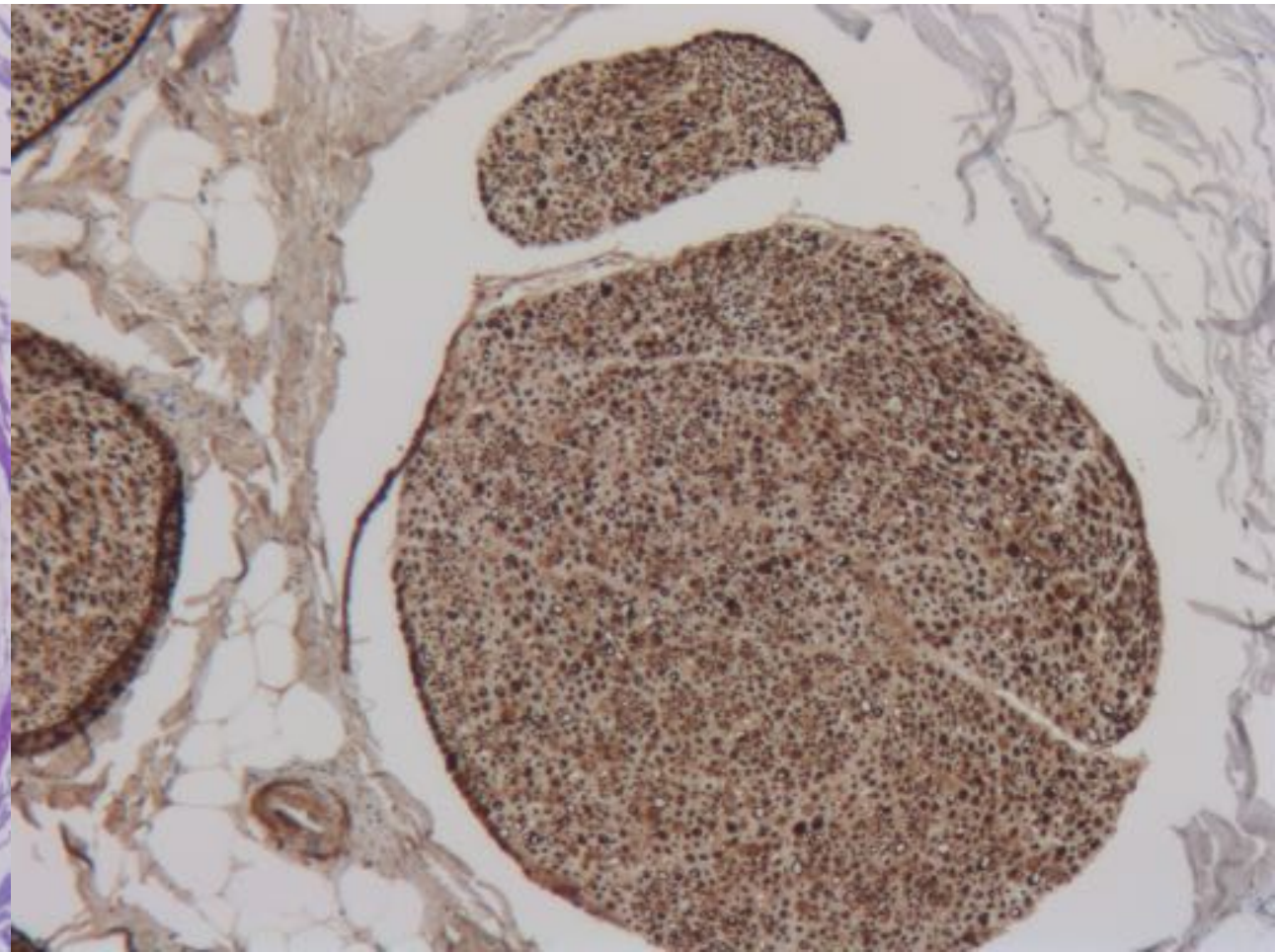

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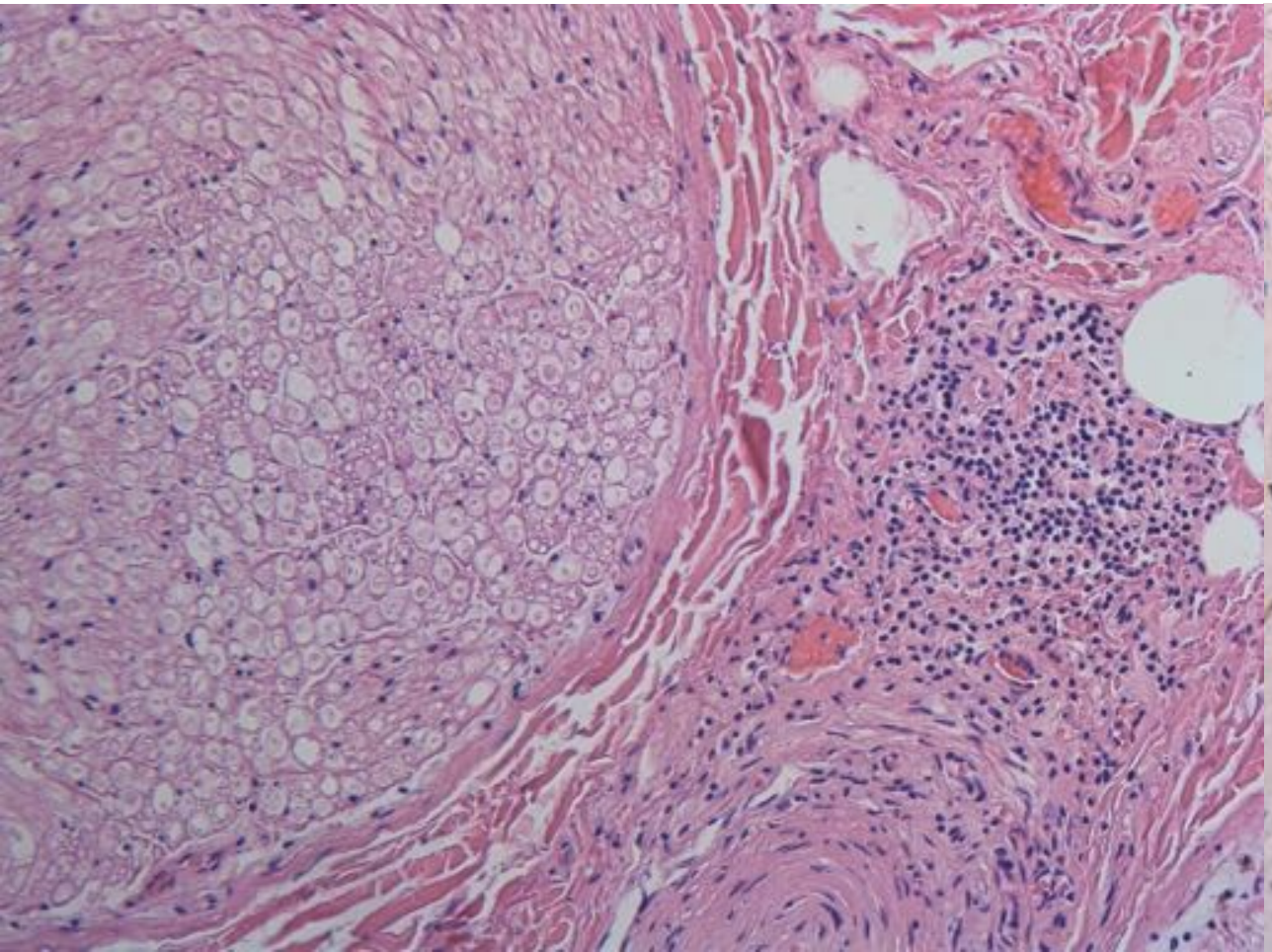

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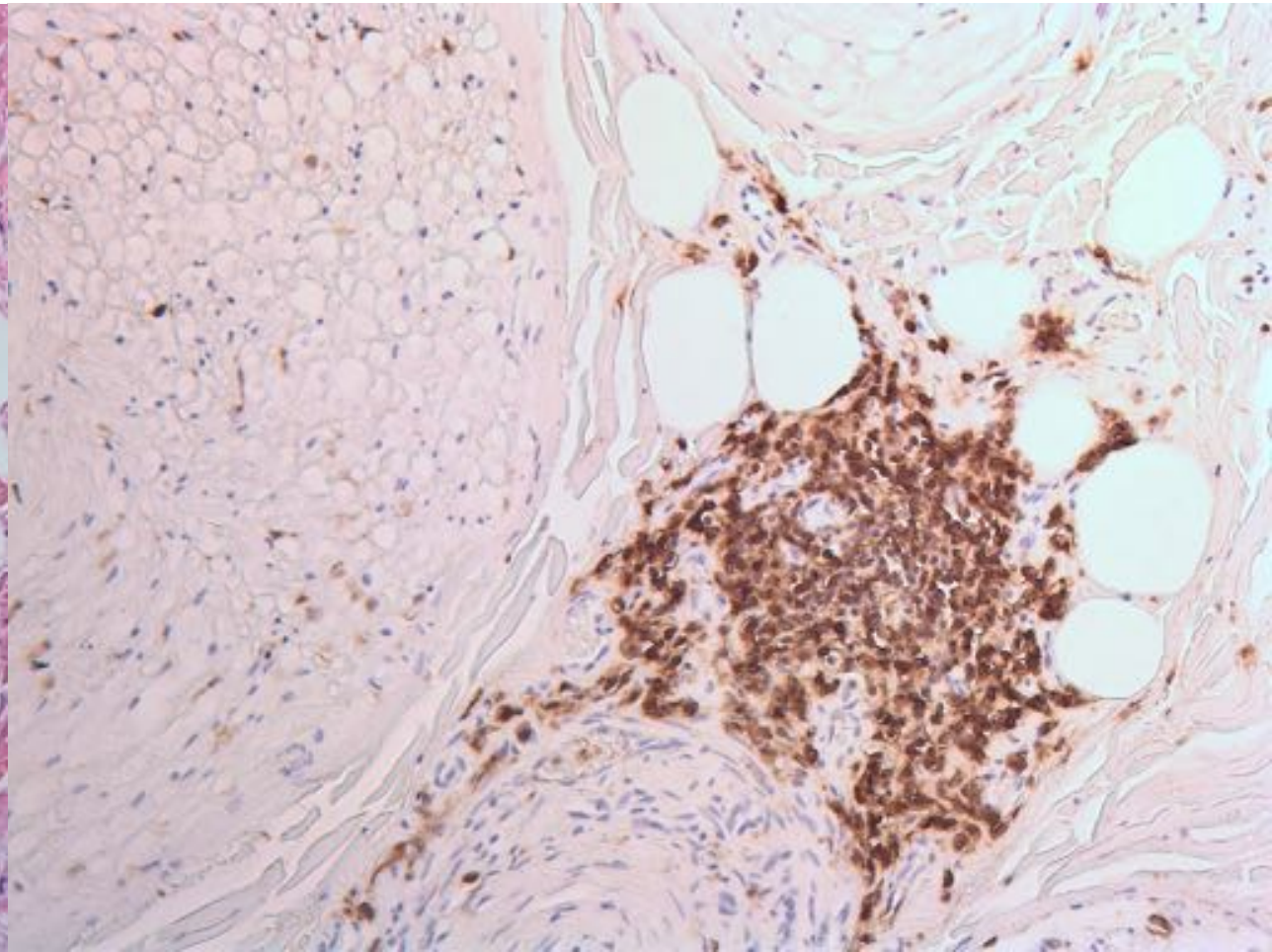

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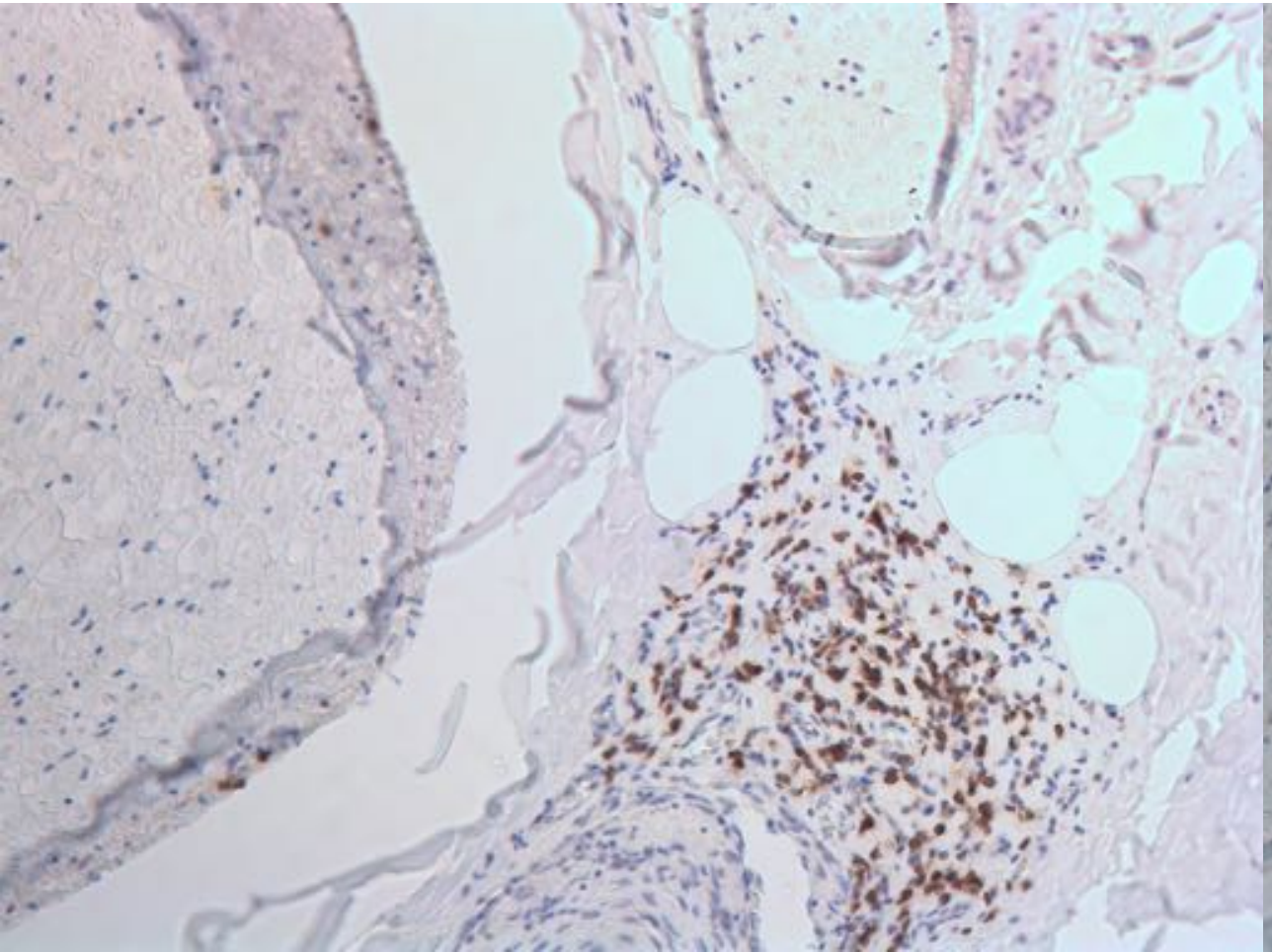

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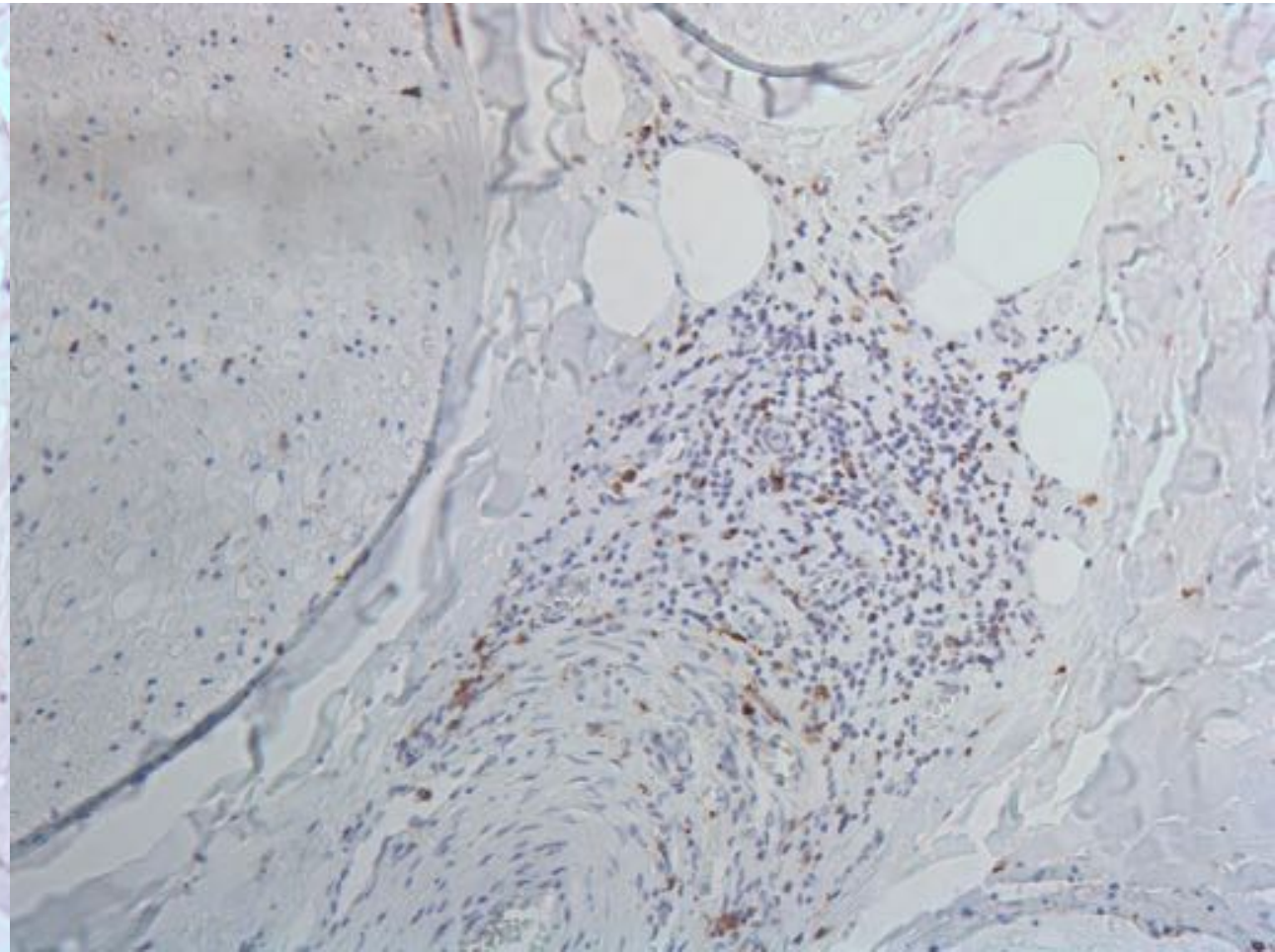

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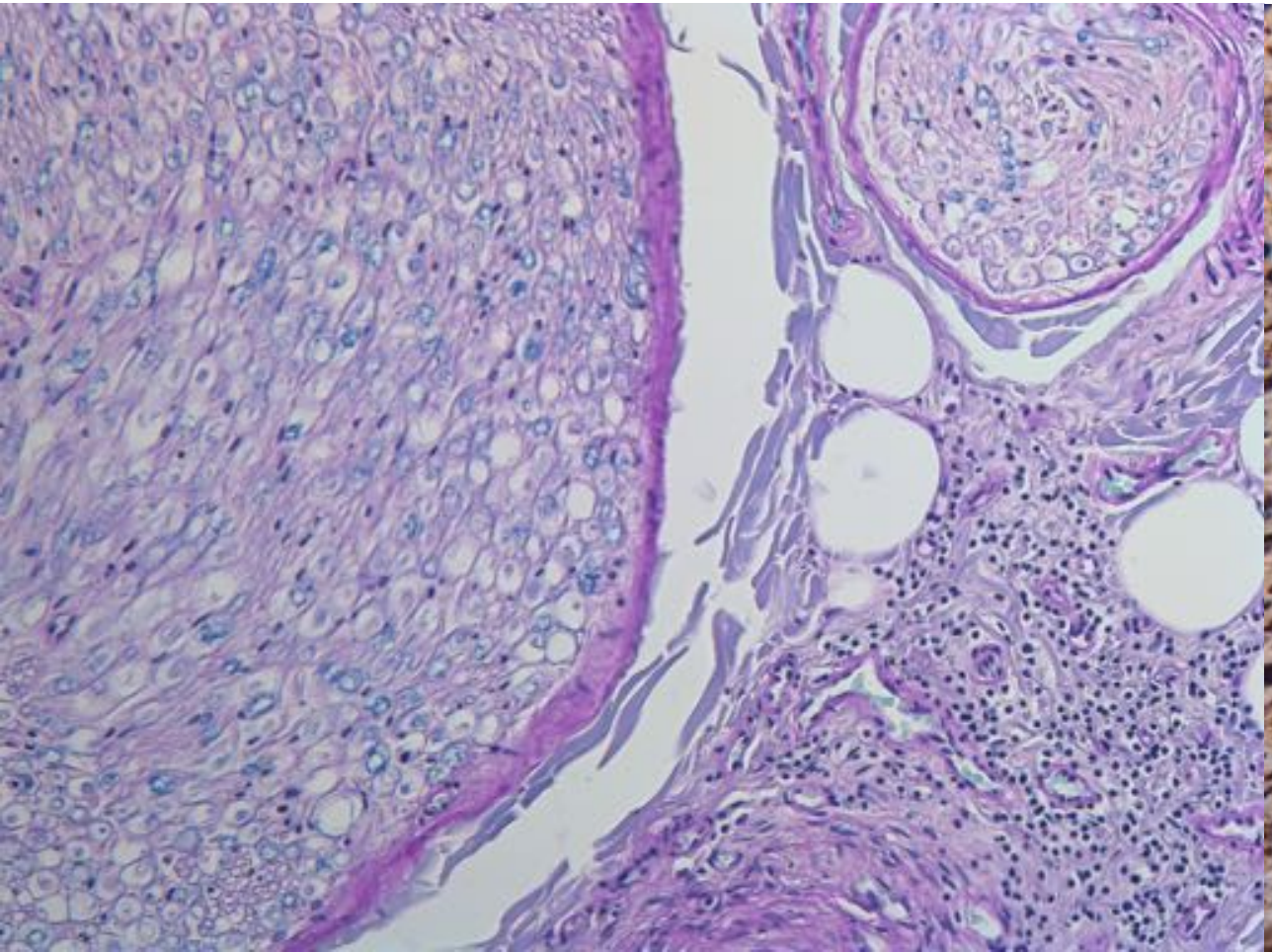
Kluver-PAS



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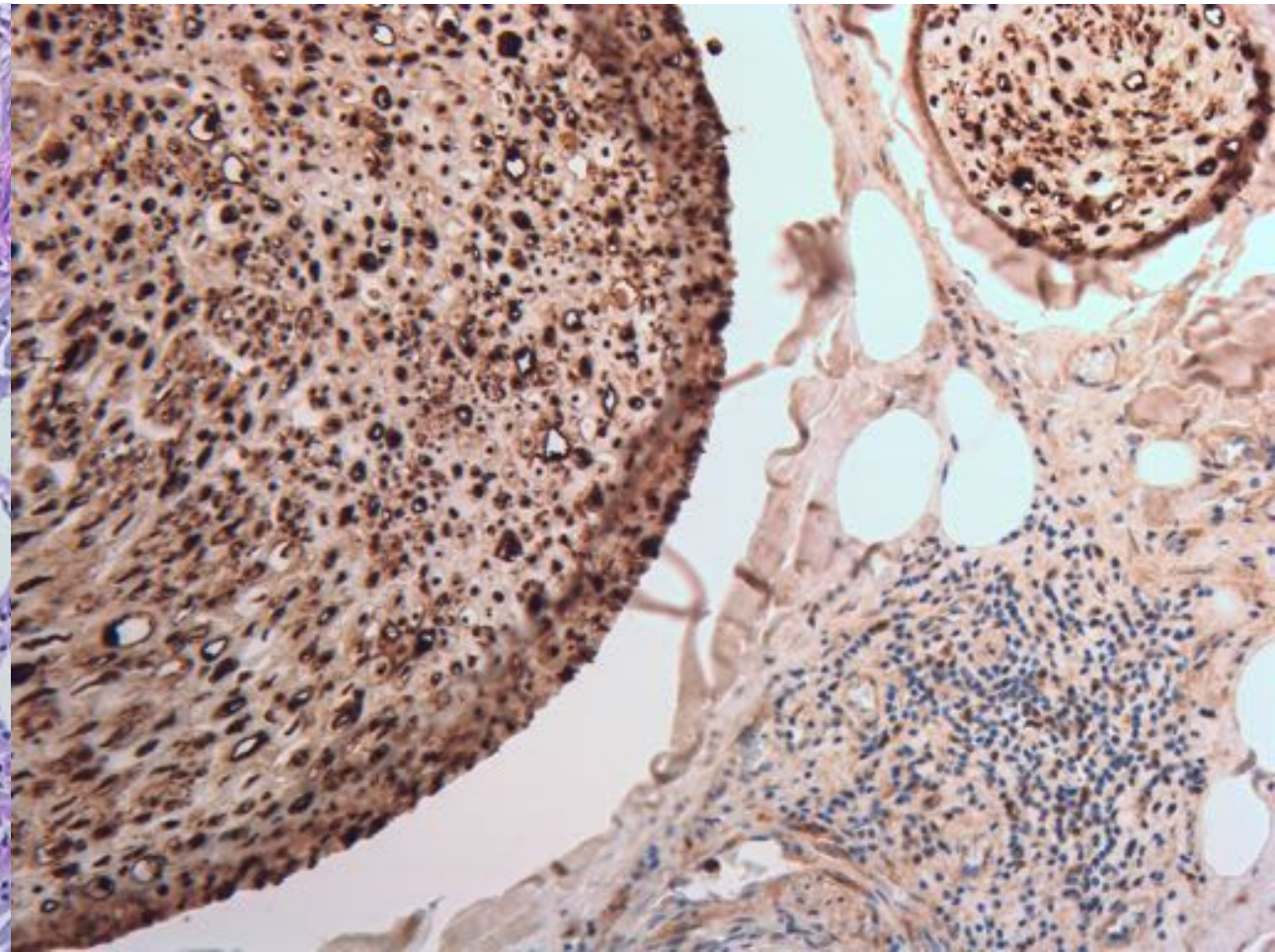

Results

- Borderline lymfocytic myocarditis in all four pilots
- Some periferal nerves show neuritis
  - Minor demyelination
  - No cytoskeletal abnormalities
- Central nervous system: no major pathology
- Other organs: no major pathology

Discussion

- Studies into the air quality in cabin and cockpit find trace amounts of TCP and TOCP
  - Levels do not exceed the safety standard, even during fume events
- Other factors
  - shift work
  - changing time zones
  - long working hours
  - cosmic radiation
  - pathogens
  - pressure change
- Non-specific and common symptoms

Discussion

- Organophosphate-Induced Delayed Polyneuropathy (OPIDP)
  - Neuropathology:
    - CNS: distal axonal degeneration, axonal loss, neuronal loss in pyramidal tracts and dorsal columns
    - PNS: distal axonal degeneration

- Chronic Organophosphate-Induced Neuropsychiatric Disorders (COPIND)?