NTP
National Toxicology Program

Pathology Peer Review Process and Selected Lesions for the 2-Year Study of Cell Phone Radiofrequency Radiation in Rats

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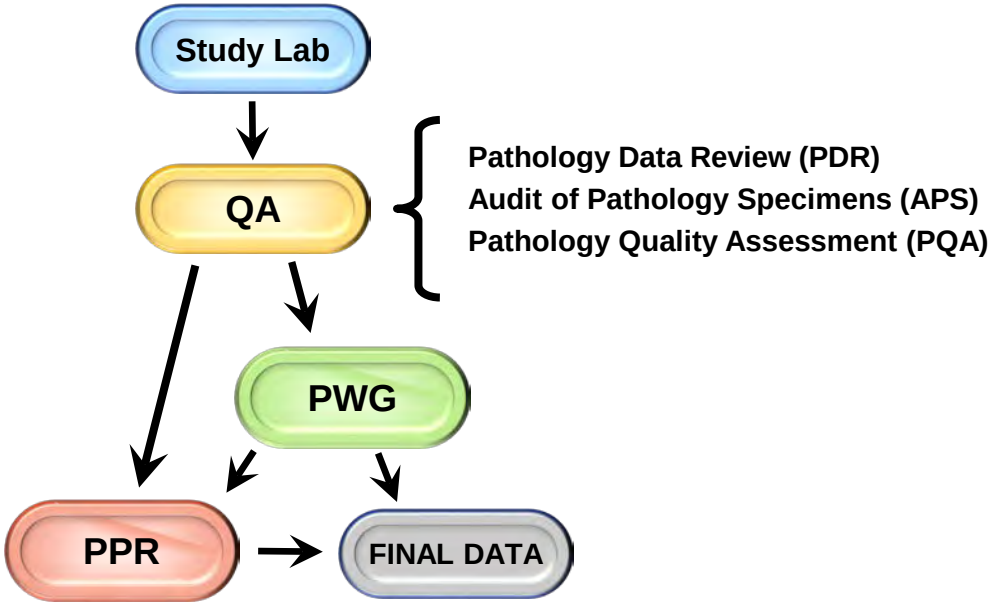
NTP Technical Report Peer-Review Meeting
March 26-28, 2018

Outline

- Pathology peer review process for the 2-year cell phone radiofrequency radiation (RFR) study in rats
- Heart, brain, and kidney lesions in the 2-year cell phone RFR study in rats

Standard NTP Pathology Peer Review Process

1. Pathology Data Review (PDR)
2. Audit of Pathology Specimens (APS)
3. Quality Assessment Review (QA)
4. Pathology Working Group (PWG)
5. +/- Pathology Peer Review (PPR)



Cell Phone Pathology Peer Review Process

- Potential treatment-related proliferative heart and brain lesions were initially selected for early reporting (i.e., partial report)
  - Complete review of these lesions (APS, PDR, QA, PWG) was conducted
    - 100% of materials reviewed in Audit of Pathology Specimens
  - Expedited review due to potential public health importance
    - Assigned multiple pathologists
    - Rapid turnaround

Cell Phone Pathology Peer Review Process

- Four Pathology Working Groups (PWGs) were convened
  - Initial PWGs were conducted as part of our normal process and underscored the need to develop definitive diagnostic criteria for these lesions
  - Two additional PWGs composed of specialists in neuro- and cardiovascular pathology conducted to develop these criteria
    - 5 external expert neuropathologists, including an MD pathologist with expertise in proliferative glial cell lesions in humans
    - 5 external expert cardiovascular pathologists

Cell Phone Pathology Peer Review Process

- After release of the partial report, the remaining tissues were reviewed according to our normal peer review process
- Several pathology peer reviews were conducted to address outstanding issues – some of these issues included data from the partial report

Cell Phone Pathology Peer Review Process

- All lesions that were potentially treatment-related were reviewed by panels of expert pathologists and the diagnoses and incidences represent a consensus of the pathology working groups

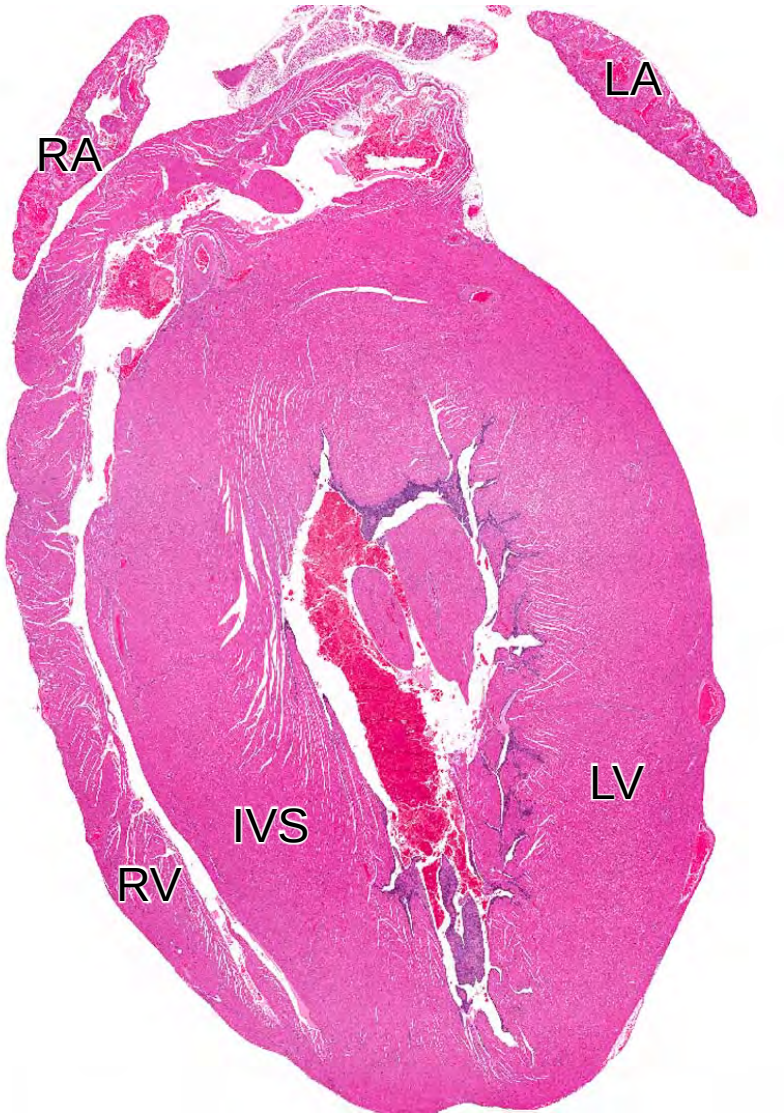
Heart, brain, and kidney lesions

- Heart
  - Schwannoma
    - Endocardial
    - Myocardial (Intramural)
  - Schwann Cell Hyperplasia
    - Endocardial
    - Myocardial (Intramural)
  - Cardiomyopathy, Right Ventricle
- Brain
  - Malignant Glioma
  - Glial Cell Hyperplasia
- Kidney - Chronic Progressive Nephropathy

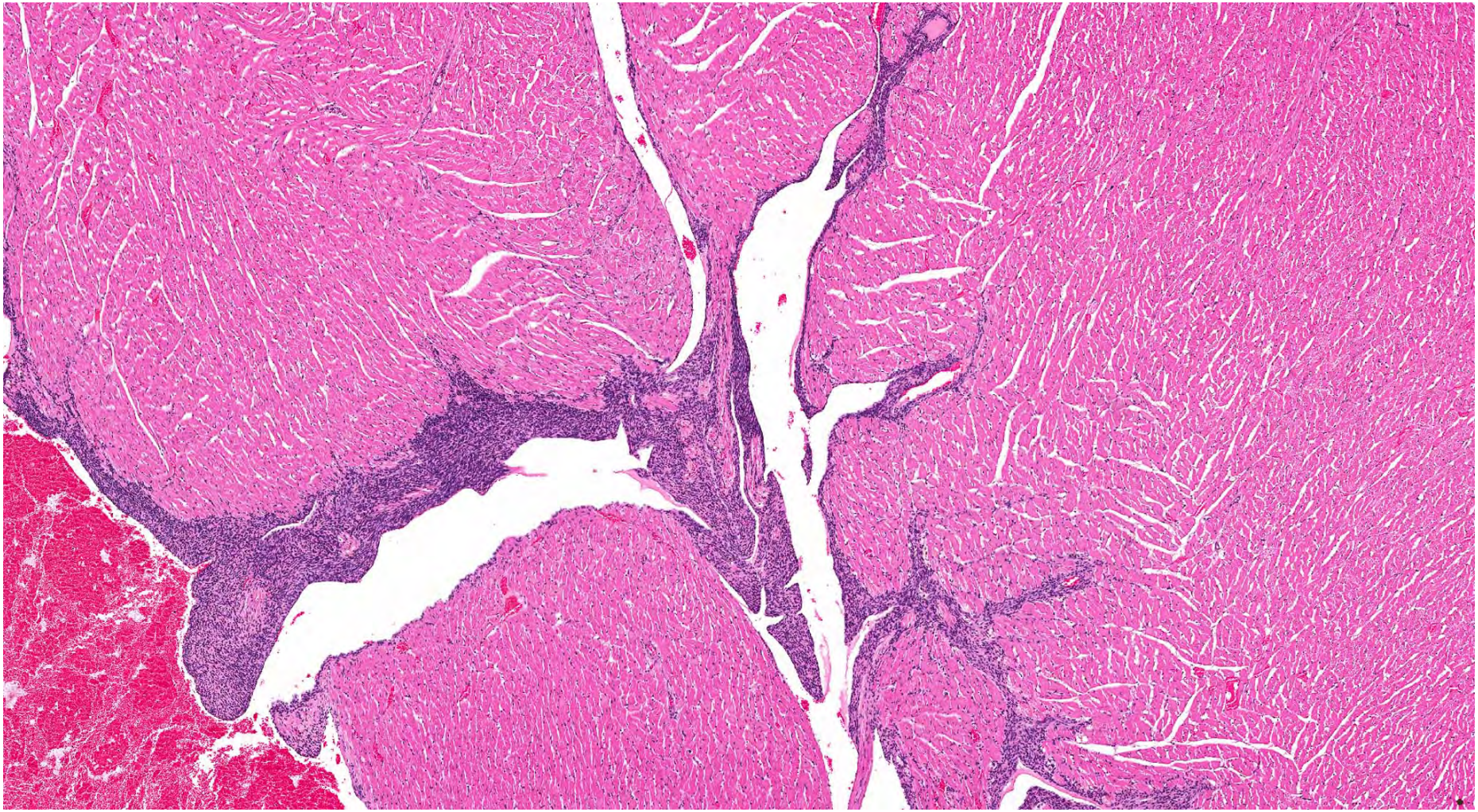
Diagnostic Criteria – Endocardial Schwannoma

- Typically arises in subendocardial region of left ventricle
- Invasive (into the myocardium)
- Cells have indistinct cell boundaries
- Usually comprises two cell types
  - Ovoid cells (typically adjacent to endocardium)
  - Spindle-shaped cells
- Cells may exhibit mild atypia
- Mitotic figures may be present
- May see palisading nuclei

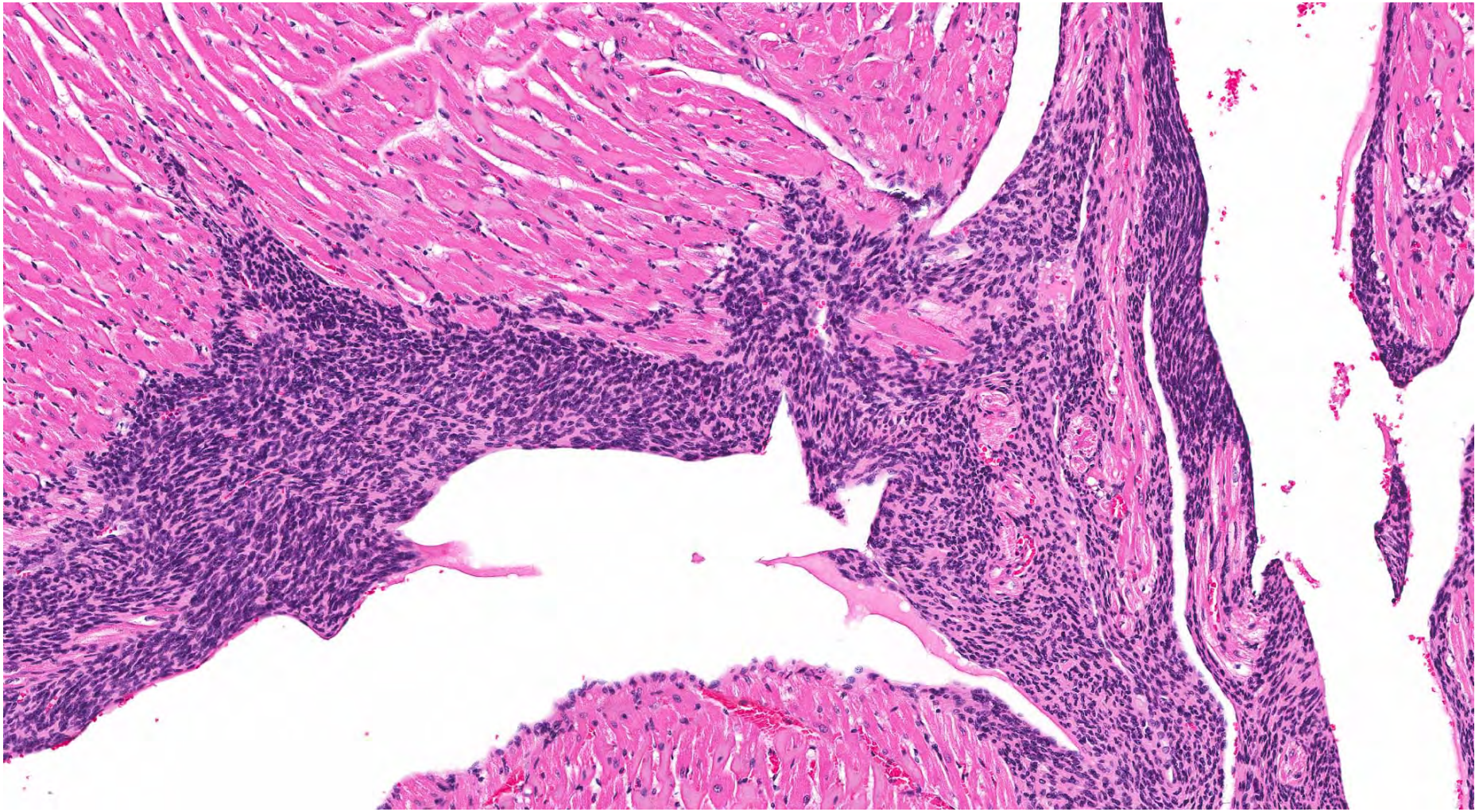
Endocardial Schwannoma



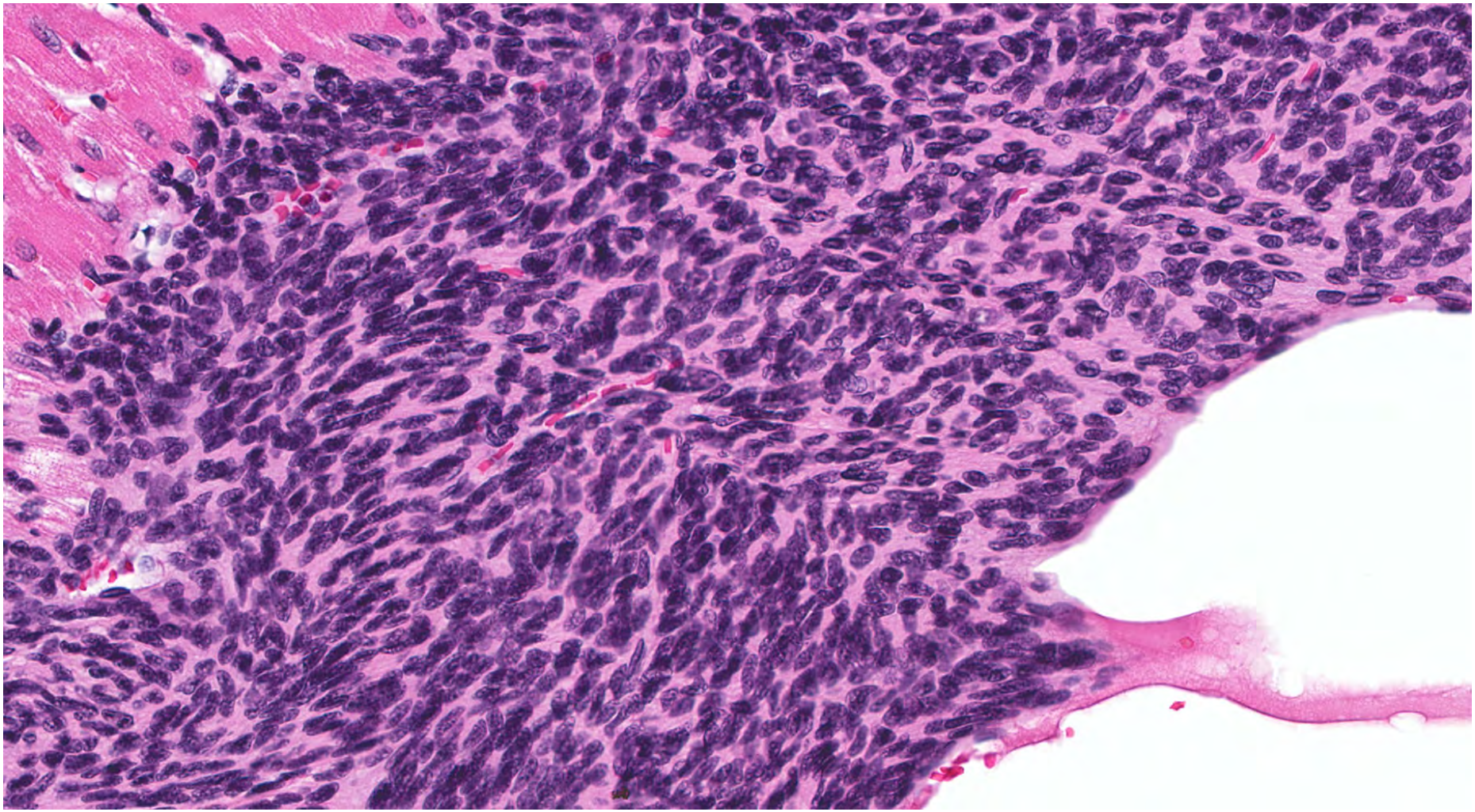
Endocardial Schwannoma



Endocardial Schwannoma



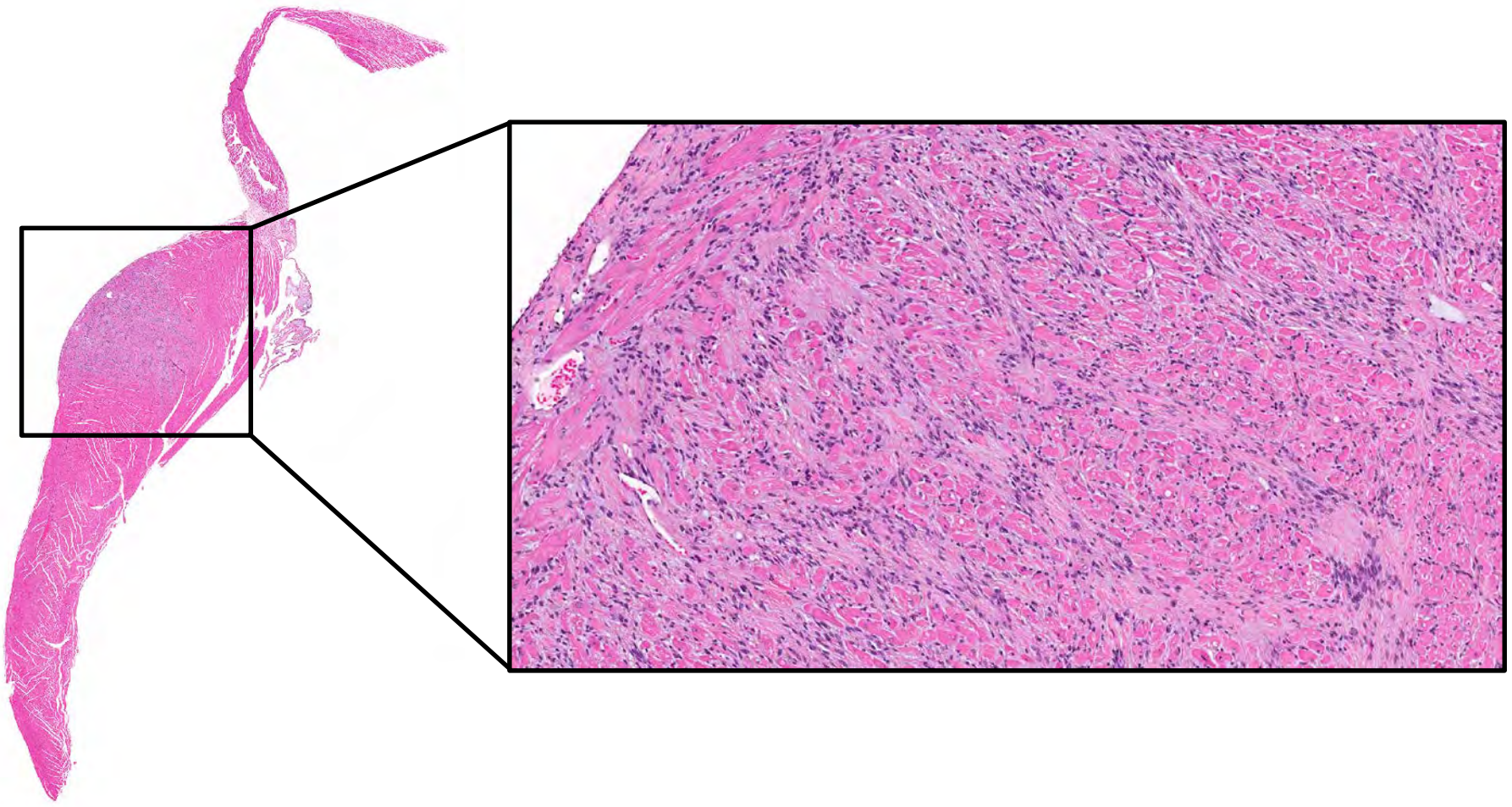
Endocardial Schwannoma



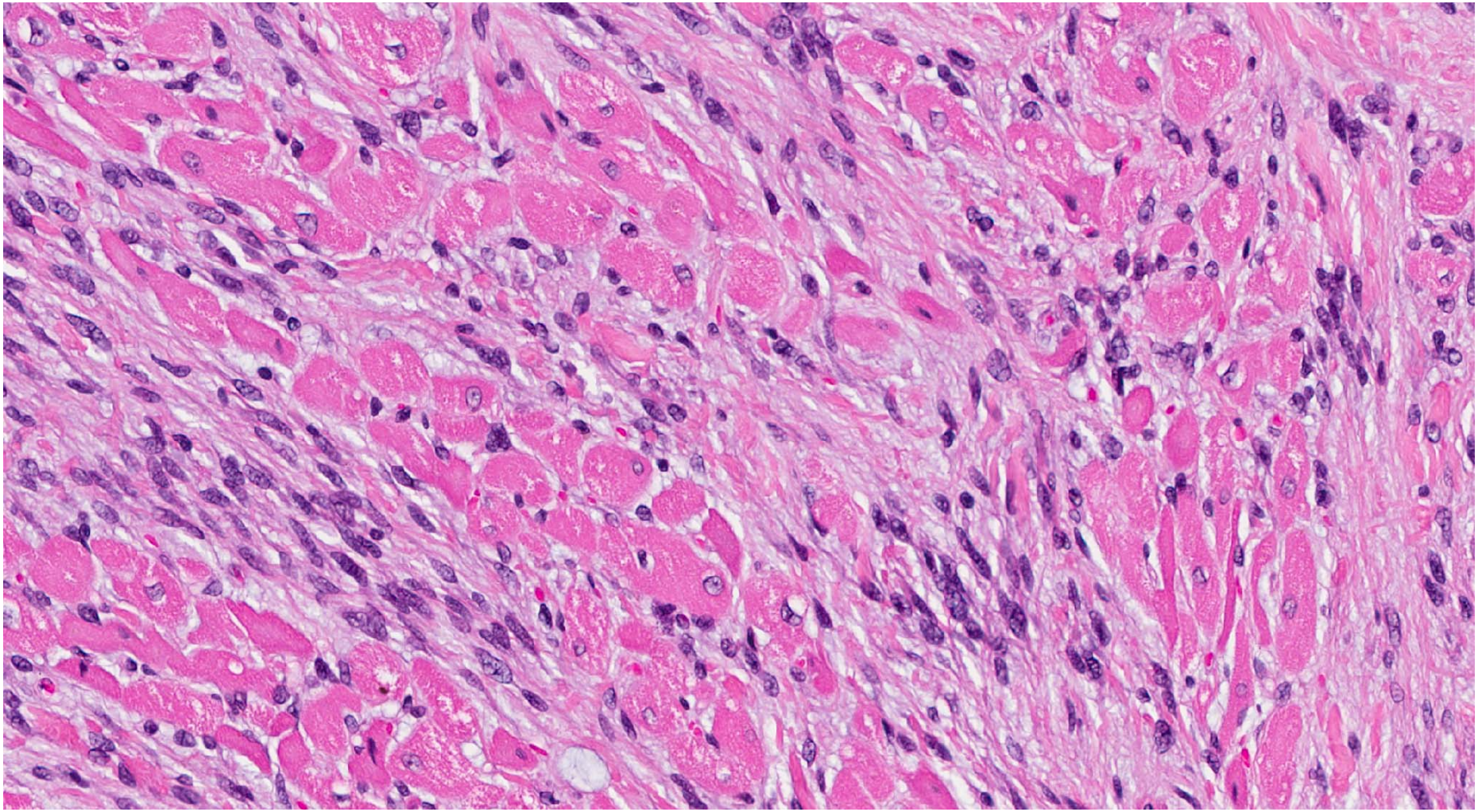
Diagnostic Criteria – Myocardial Schwannoma

- Often less cellular than endocardial schwannomas
- Lesion margins are indistinct
- Composed of loosely arranged spindle-shaped cells
- Mitotic figures and mild cellular atypia may be present
- May see palisading nuclei

Myocardial Schwannoma



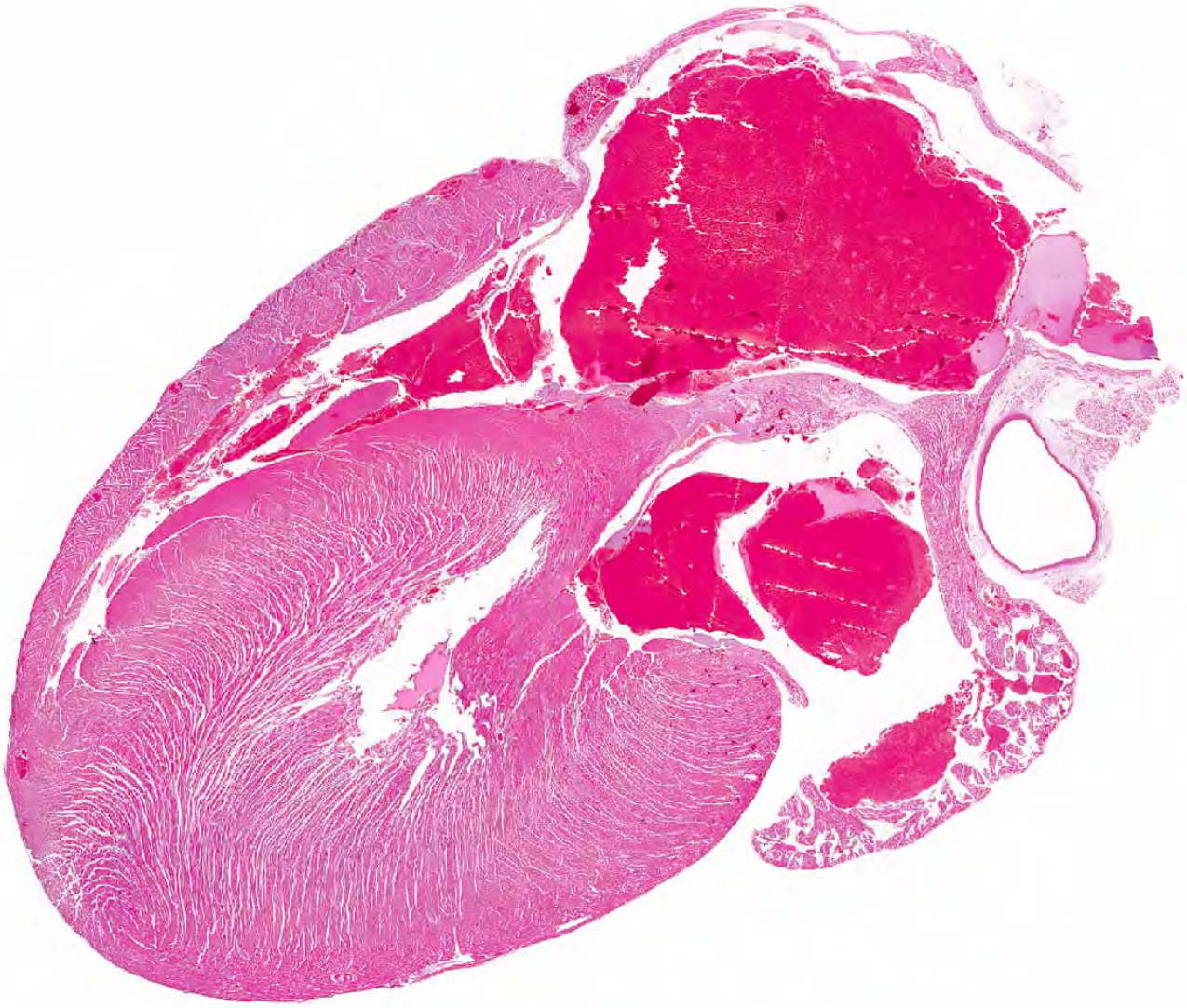
Myocardial Schwannoma



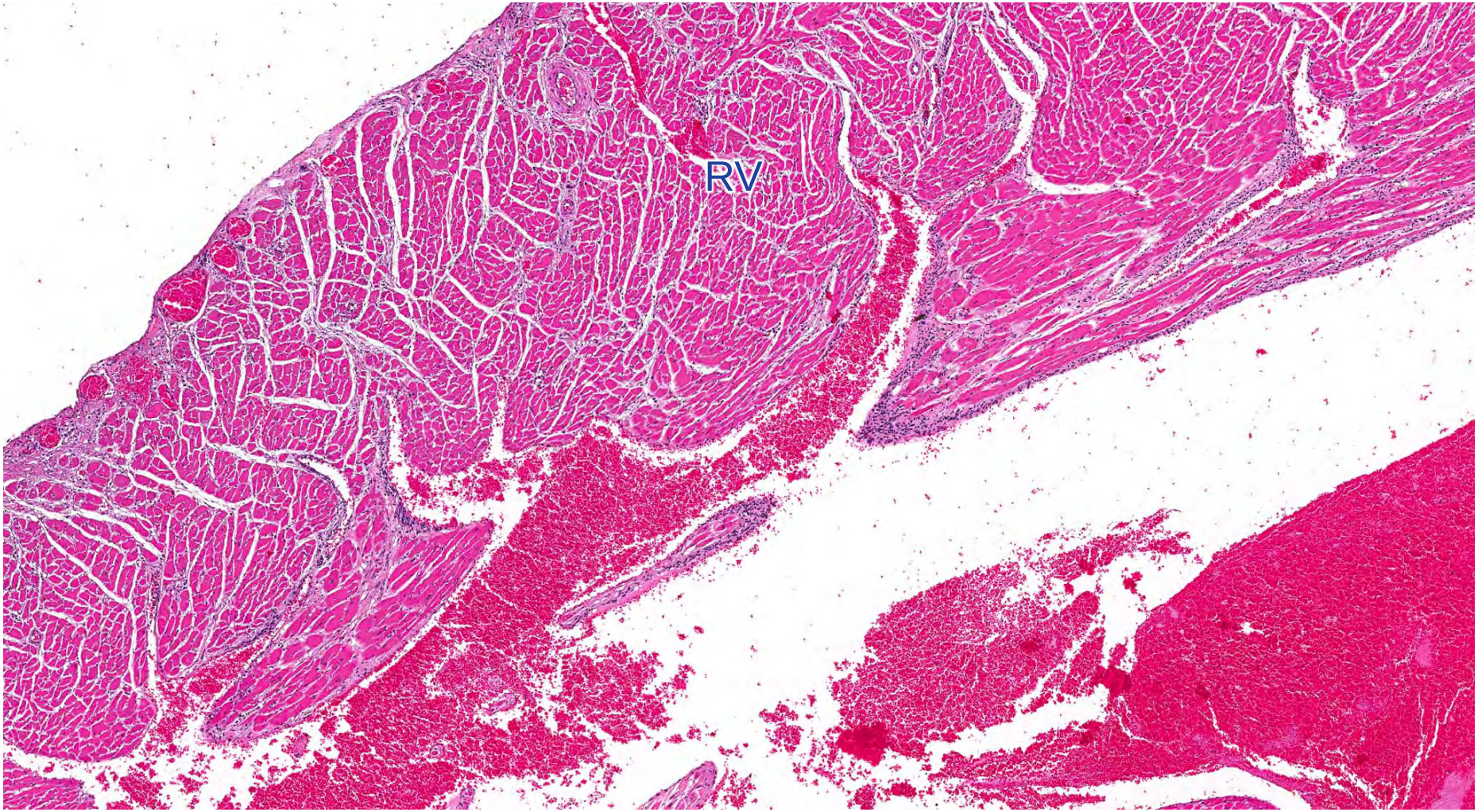
Diagnostic Criteria – Schwann Cell Hyperplasia

- Similar to Schwannoma, except:
  - Less extensive than schwannoma
  - Noninvasive (though proliferation along existing nerve tracts may give the appearance of invasion)
  - There is no cellular atypia
  - Mitotic figures are rare
- May also occur in the myocardium

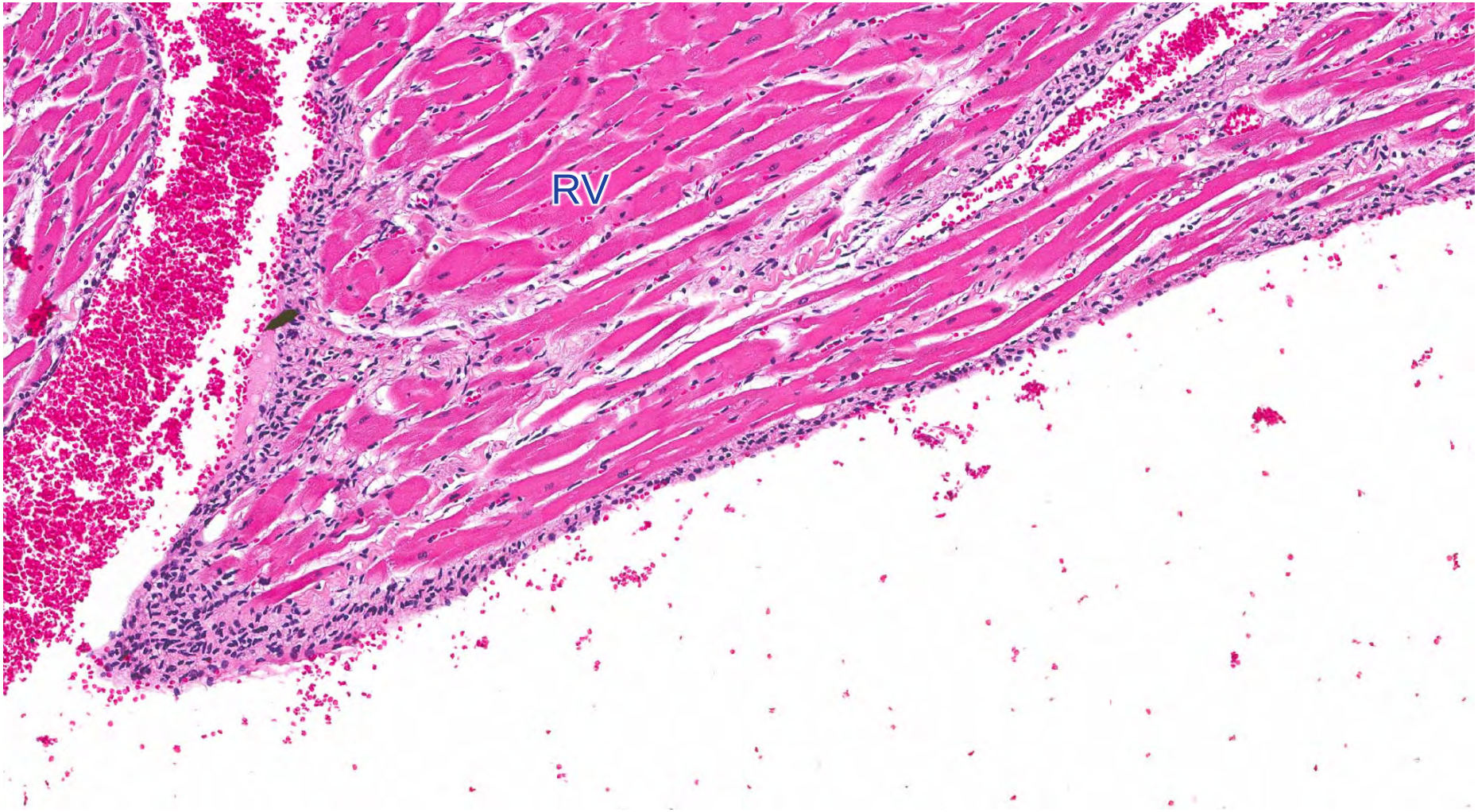
Endocardial Schwann Cell Hyperplasia



Endocardial Schwann Cell Hyperplasia



Endocardial Schwann Cell Hyperplasia

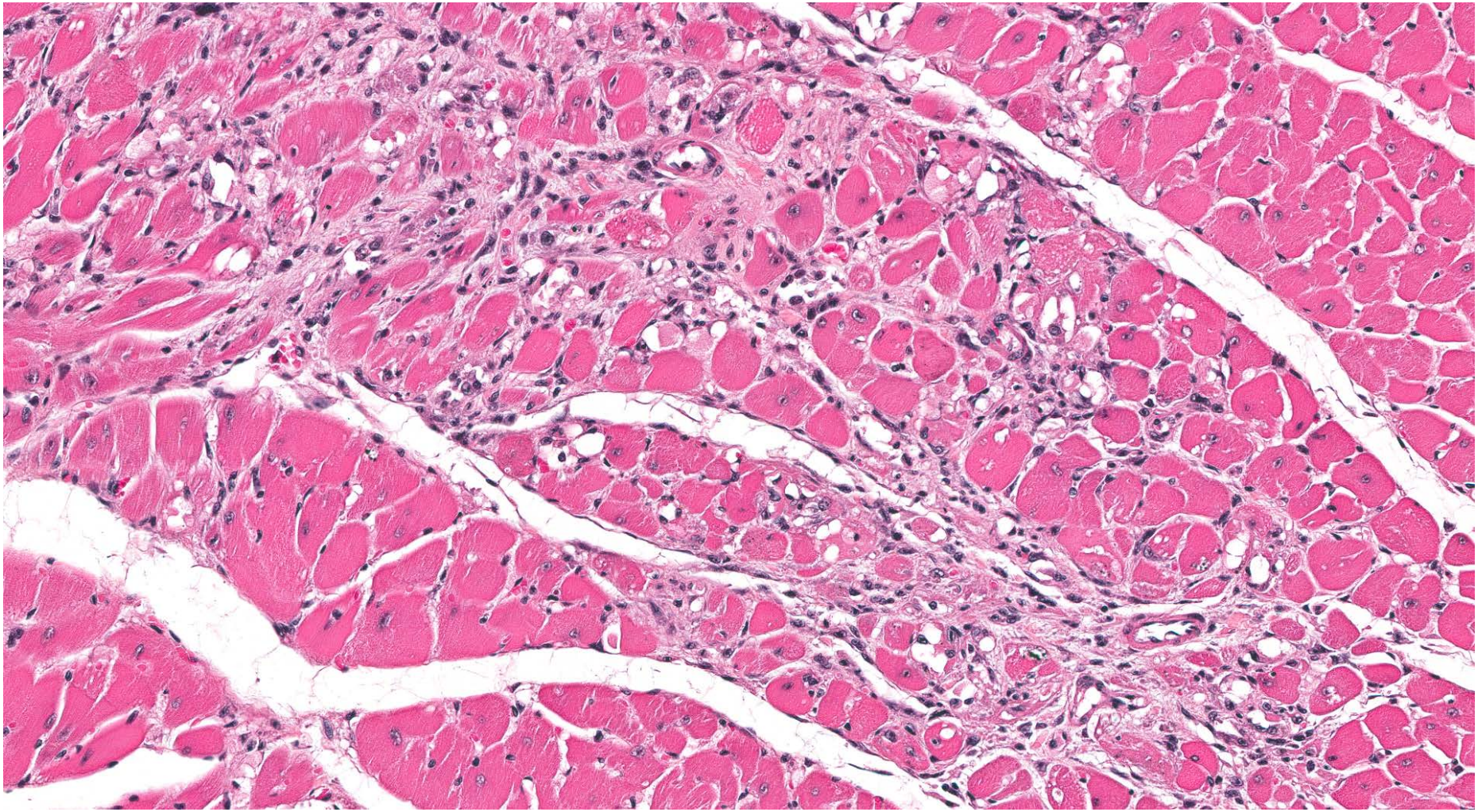


Diagnostic Criteria – Cardiomyopathy

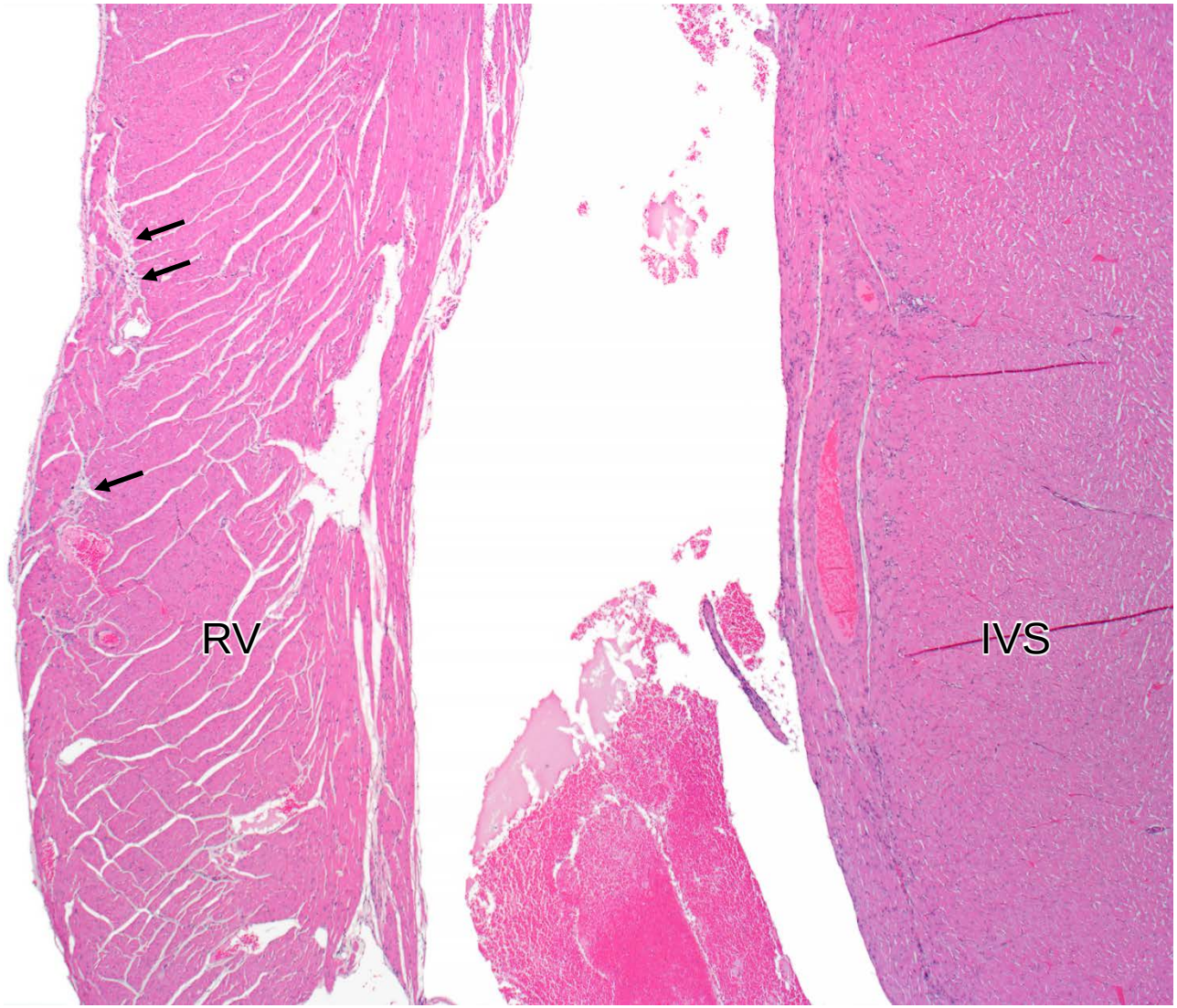
- Degeneration, necrosis, or loss of cardiomyocytes
- +/- mild inflammation – macrophages and lymphocytes with occasional neutrophils
- Fibrosis in later stages of disease
- In right ventricle, most prominent in subepicardial region in lower half of heart (toward apex)

Heart, brain, and kidney lesions

Cardiomyopathy

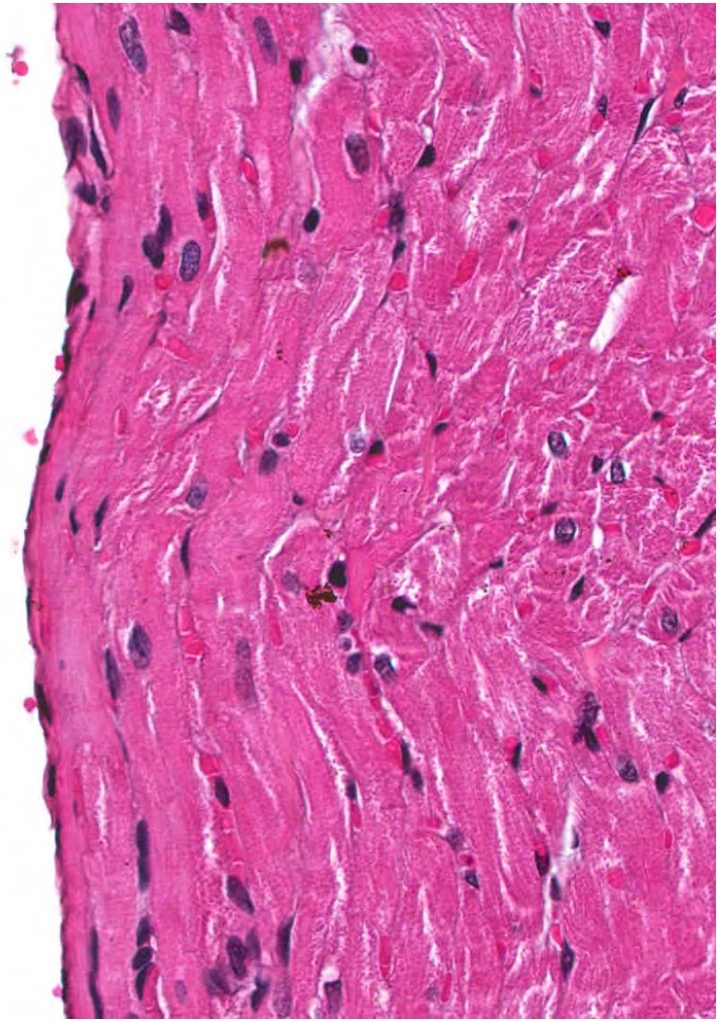


Right Ventricle – Cardiomyopathy

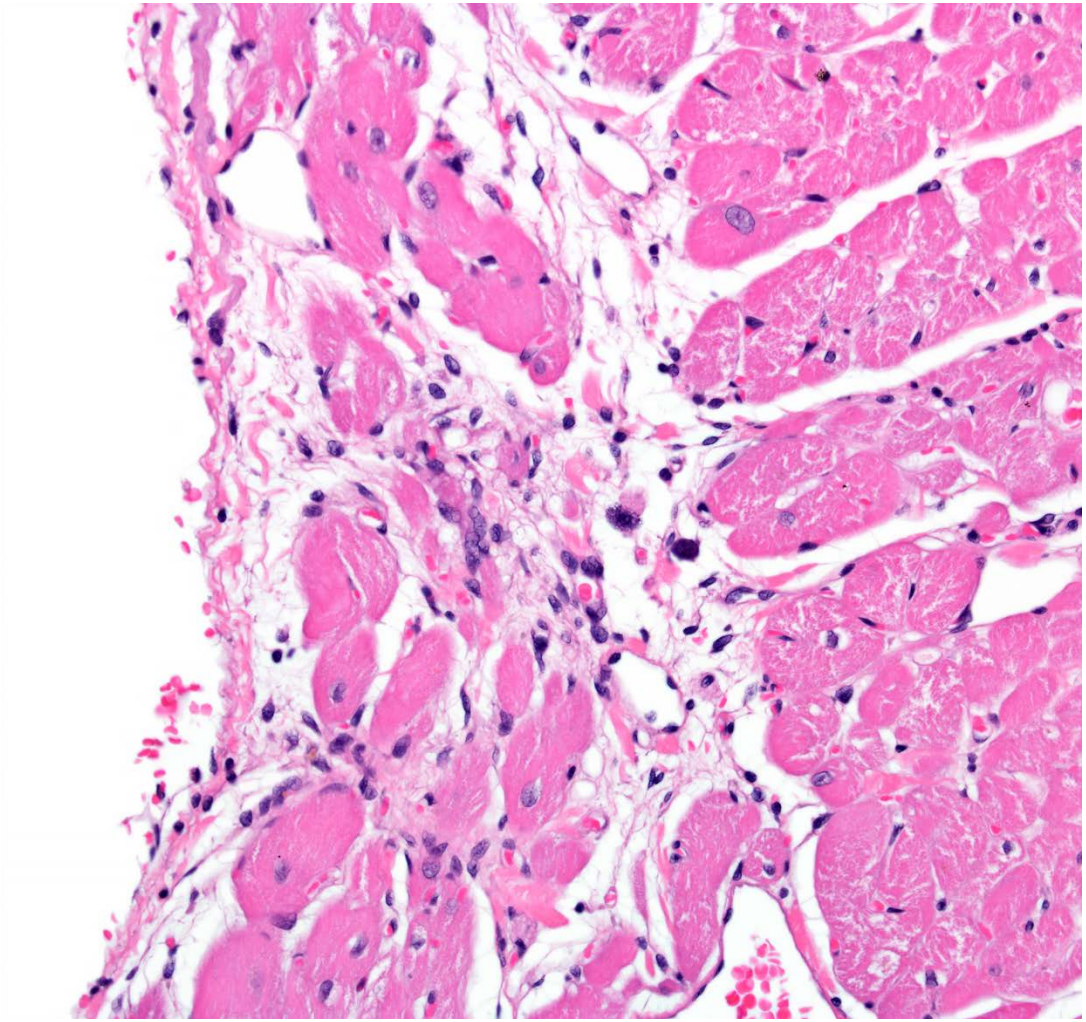


Heart, brain, and kidney lesions

Right Ventricle – Normal

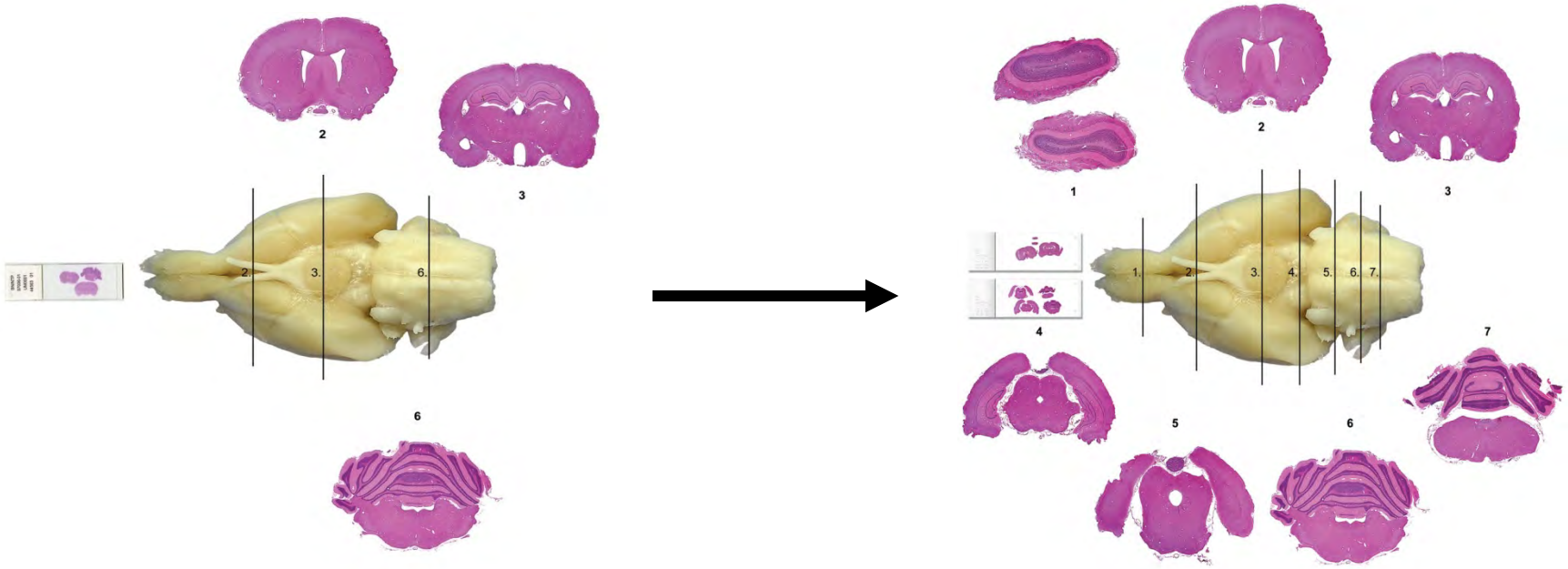


Right Ventricle – Cardiomyopathy



Brain Sampling

From 3 to 7 Sections of Brain



Original

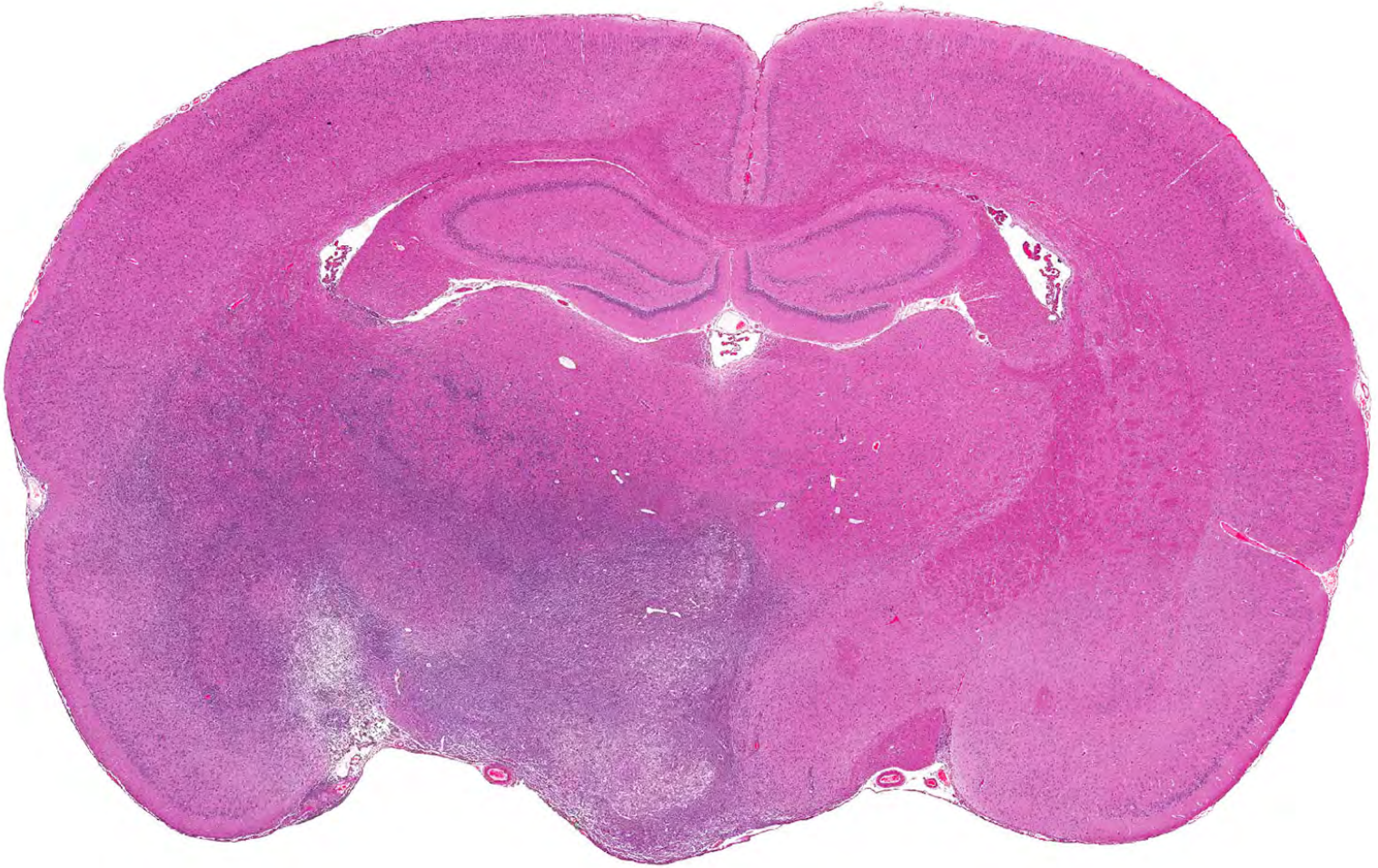
New Sampling

Diagnostic Criteria – Malignant Glioma

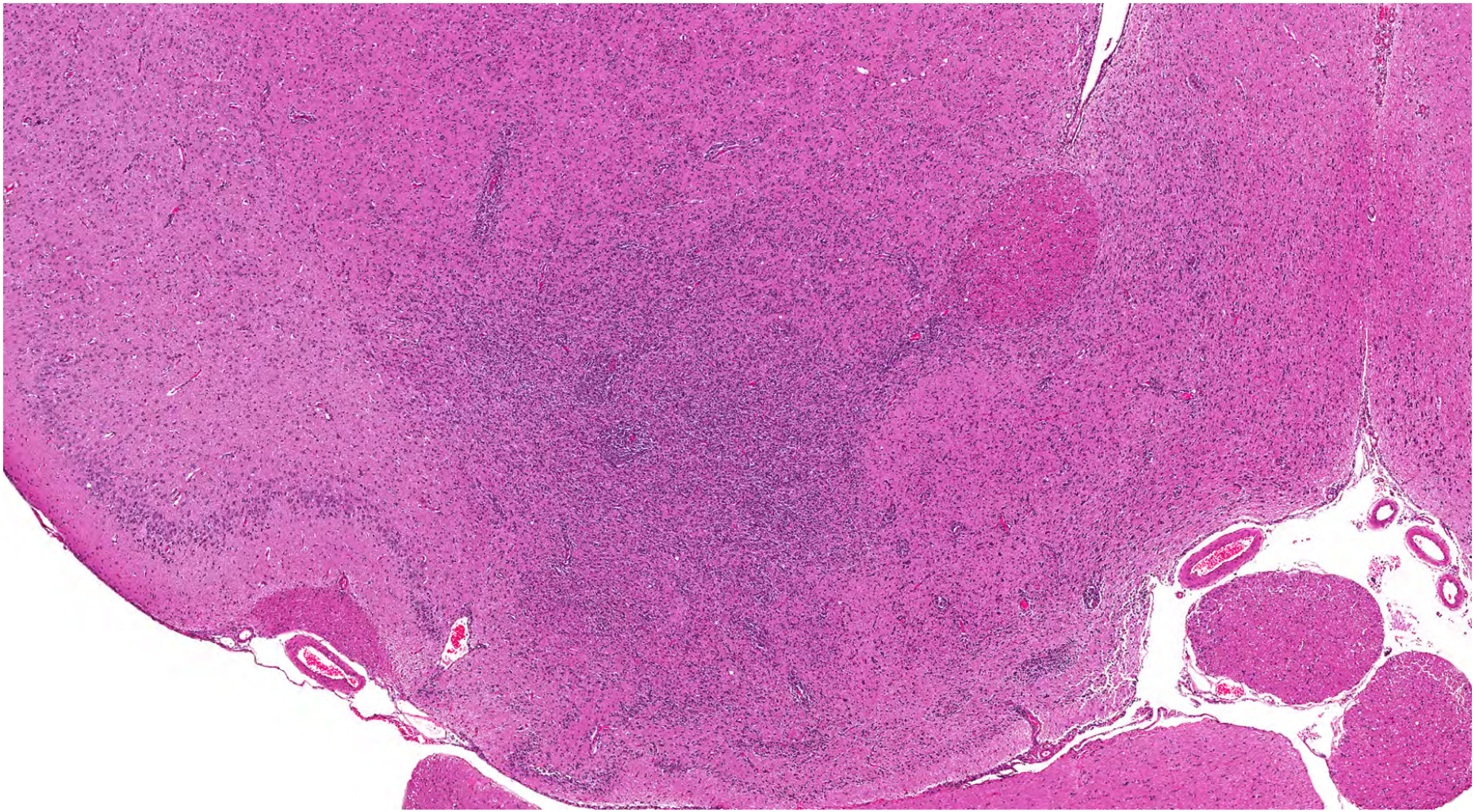
- Neoplasms are usually larger than glial cell hyperplasia
- Indistinct lesion borders
- Cells are usually pleomorphic and densely packed
- Perivascular cuffing
- +/- Satellitosis
- +/- Meningeal invasion
- +/- Mitotic figures (few)

Heart, brain, and kidney lesions

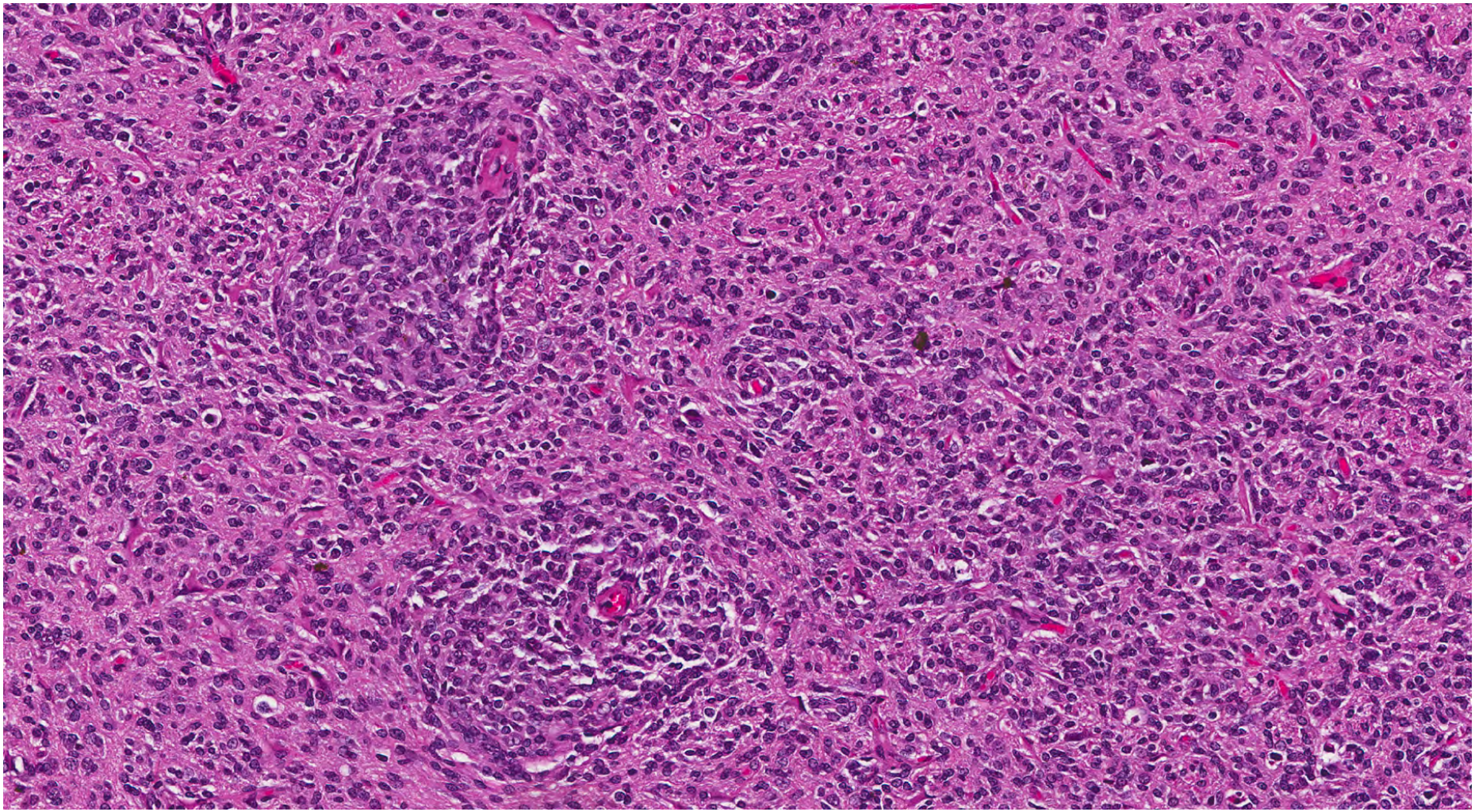
Malignant Glioma



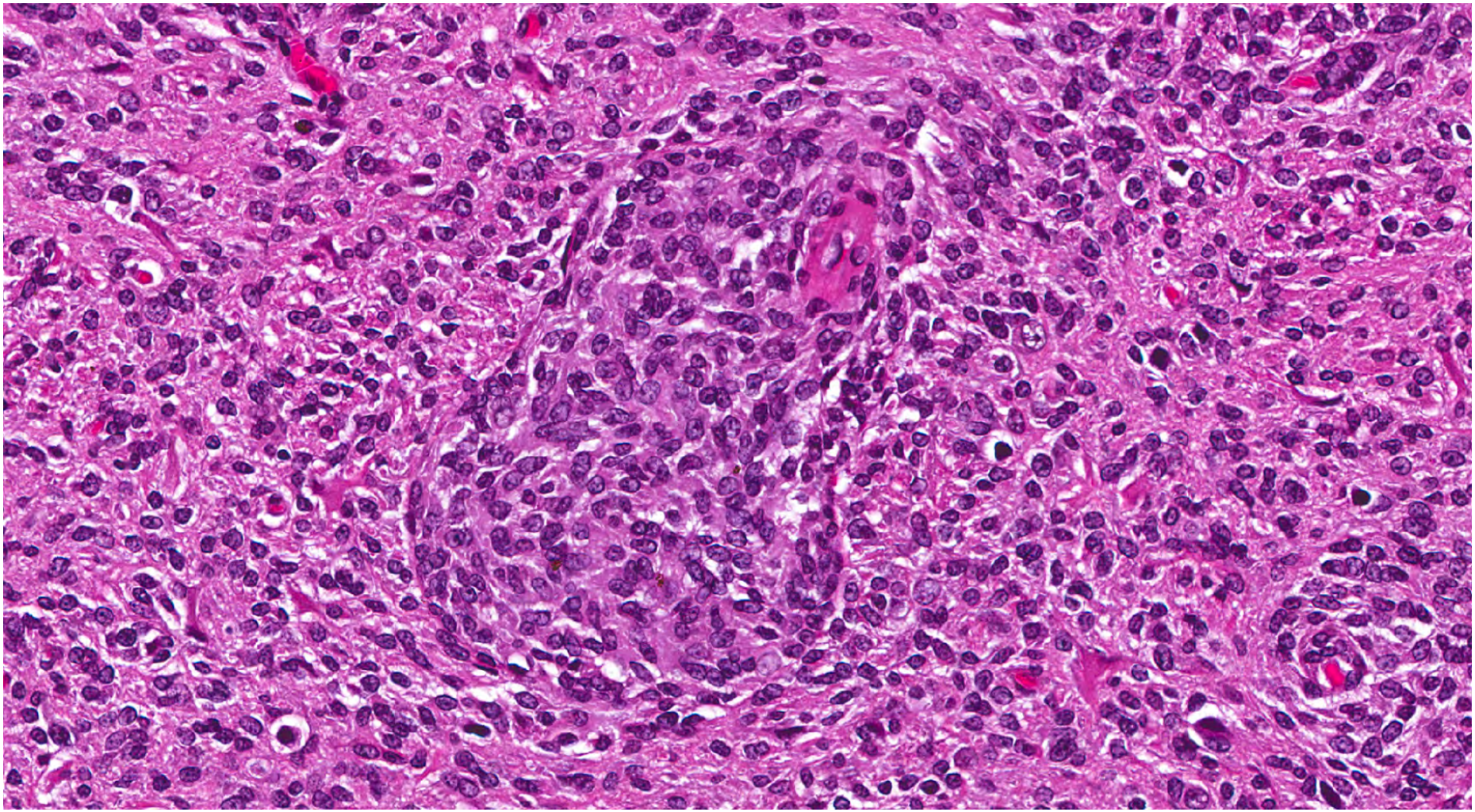
Malignant Glioma



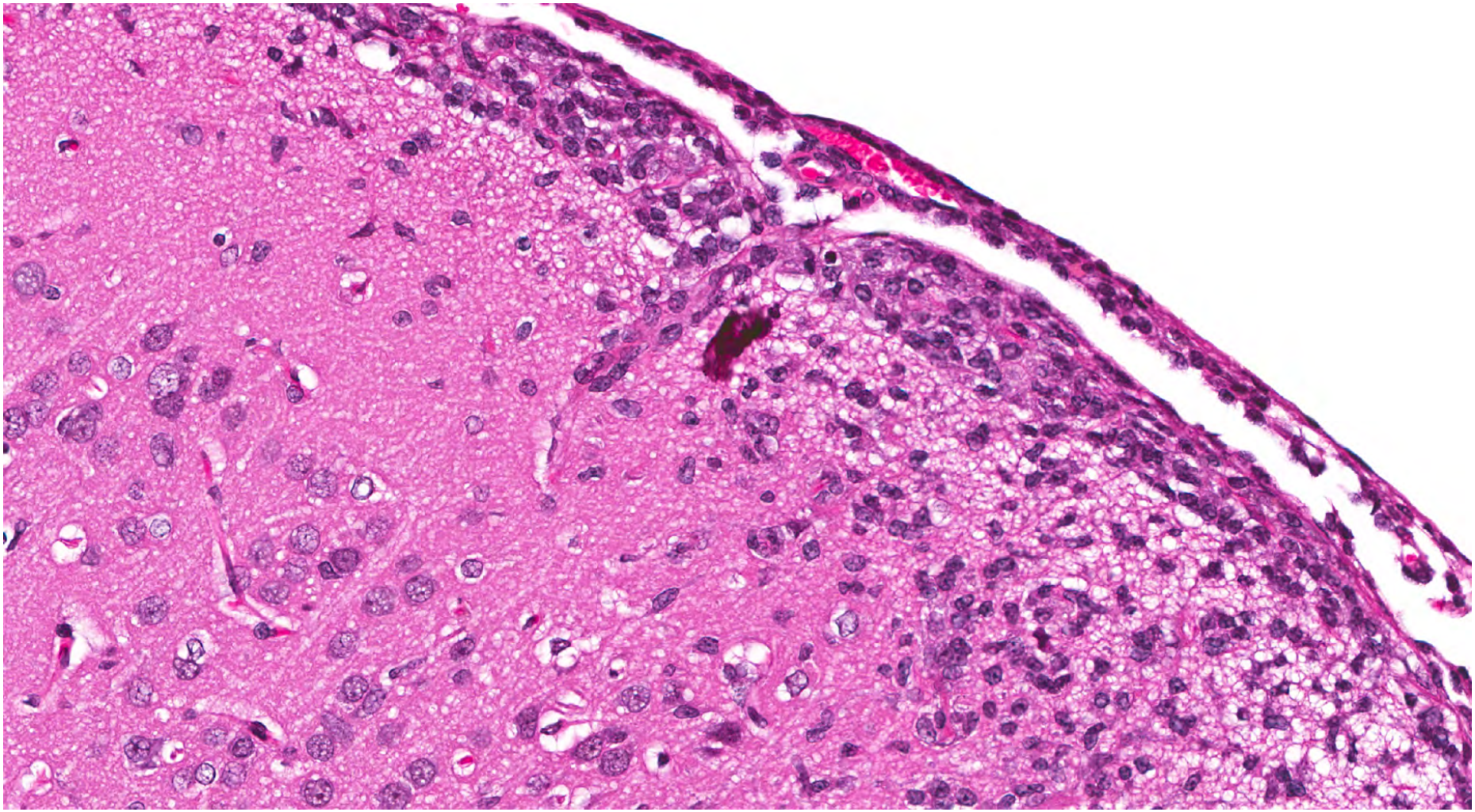
Malignant Glioma



Malignant Glioma



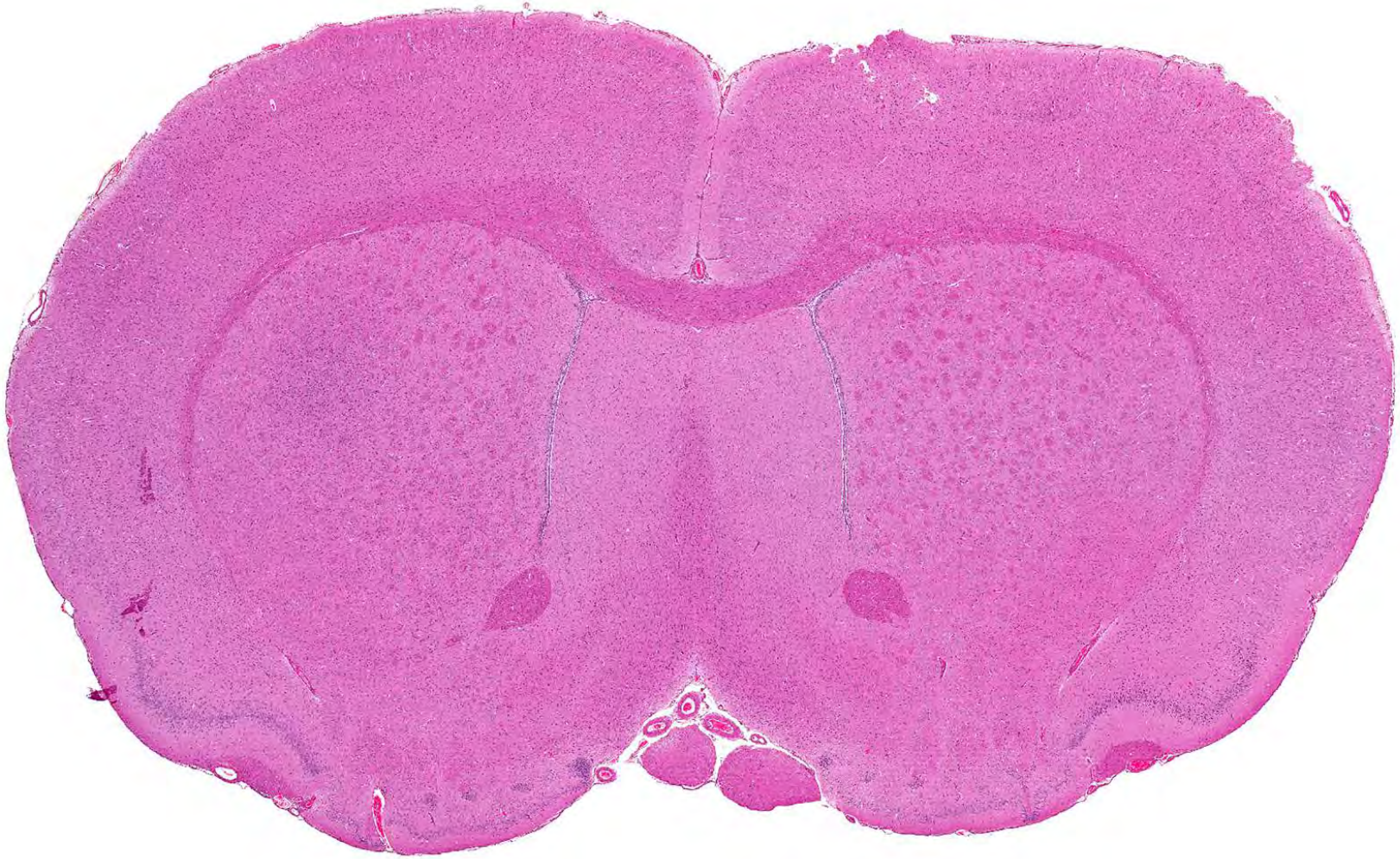
Malignant Glioma



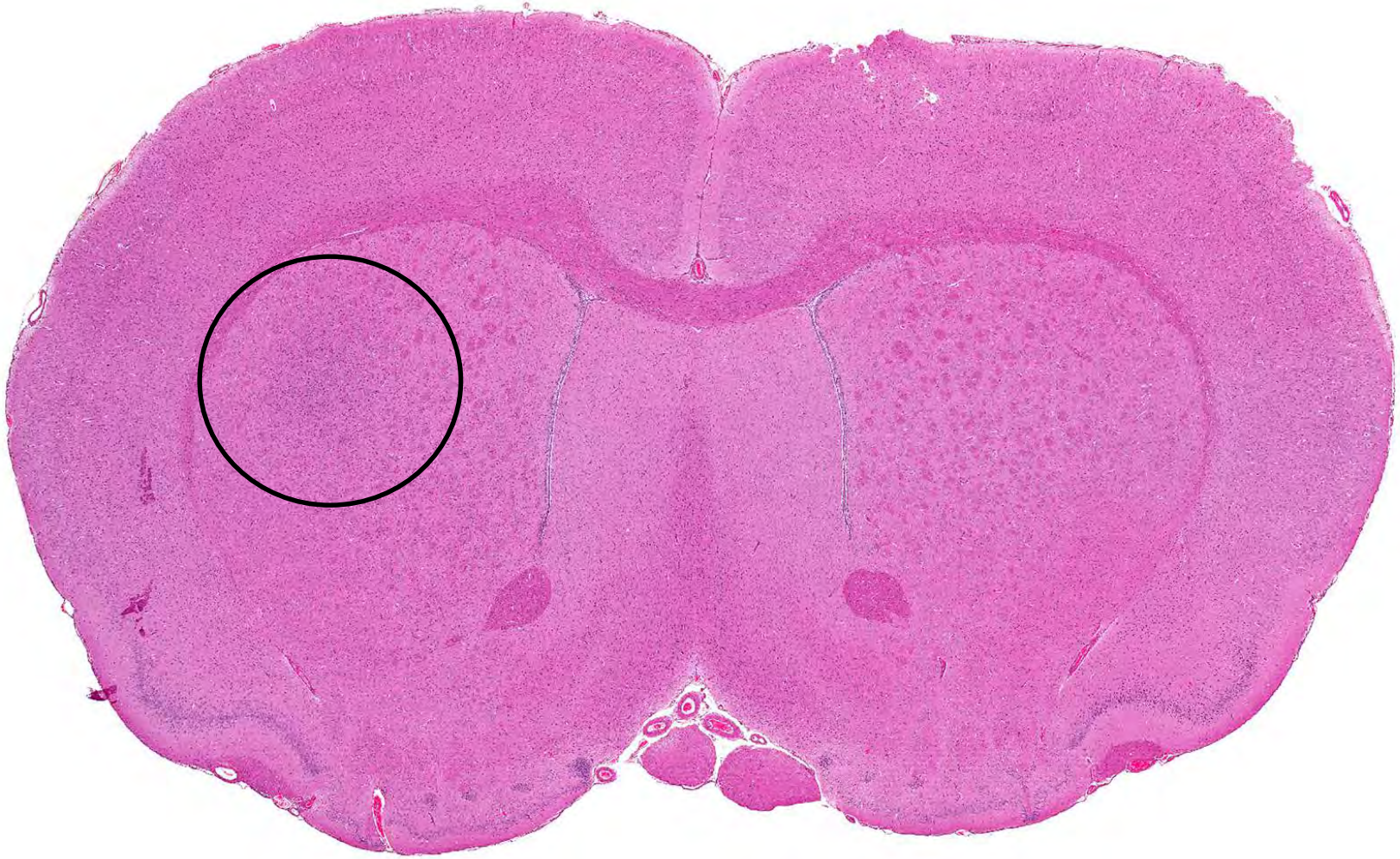
Diagnostic Criteria – Glial Cell Hyperplasia

- Similar to malignant glioma except:
  - Usually smaller
  - No meningeal invasion
  - Cell density is low
  - +/- Perivascular cuffing (minimal if present)
  - Generally, no mitotic figures
- Additionally, no reactive, degenerative, or necrotic elements with the associated parenchyma

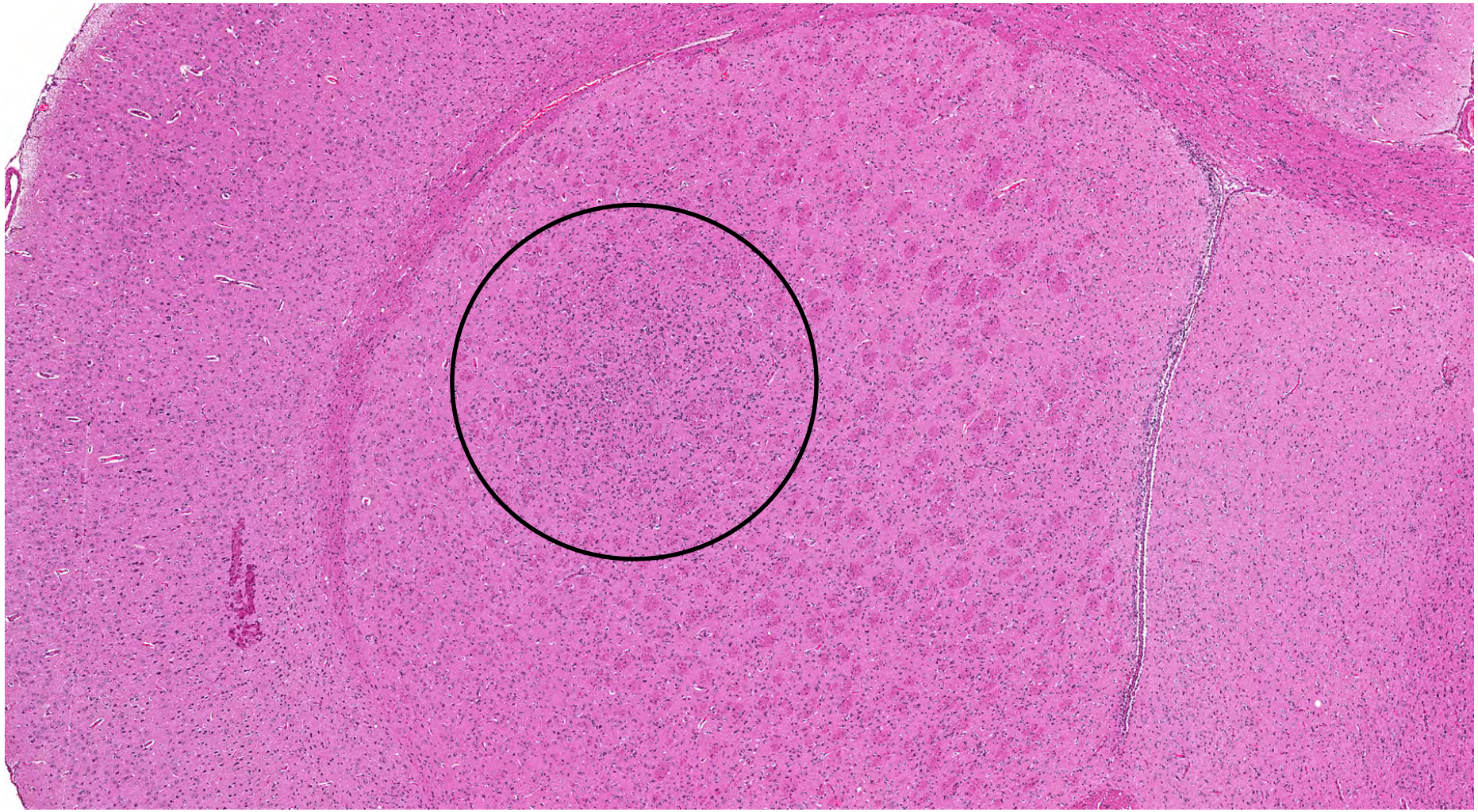
Glial Cell Hyperplasia



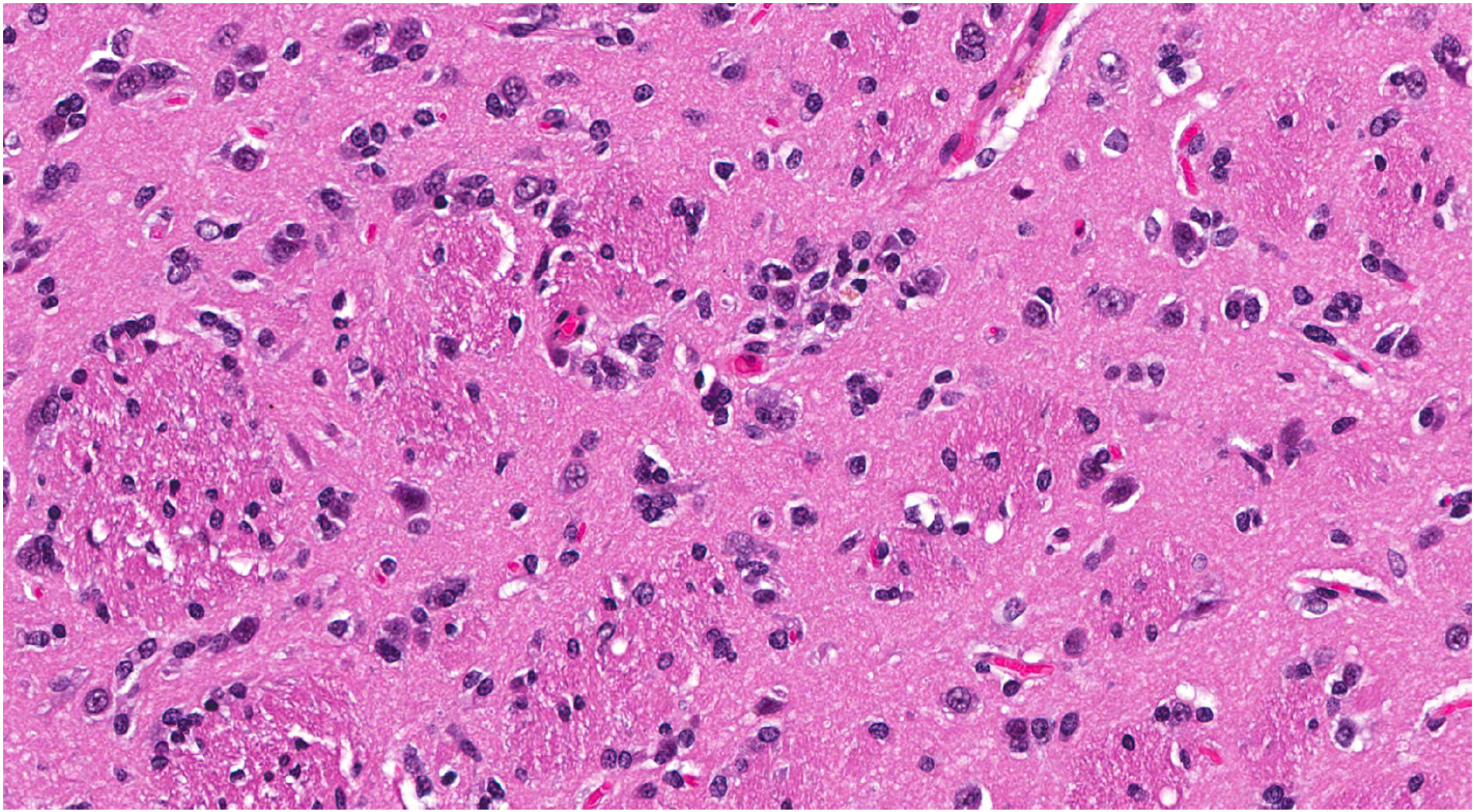
Glial Cell Hyperplasia



Glial Cell Hyperplasia

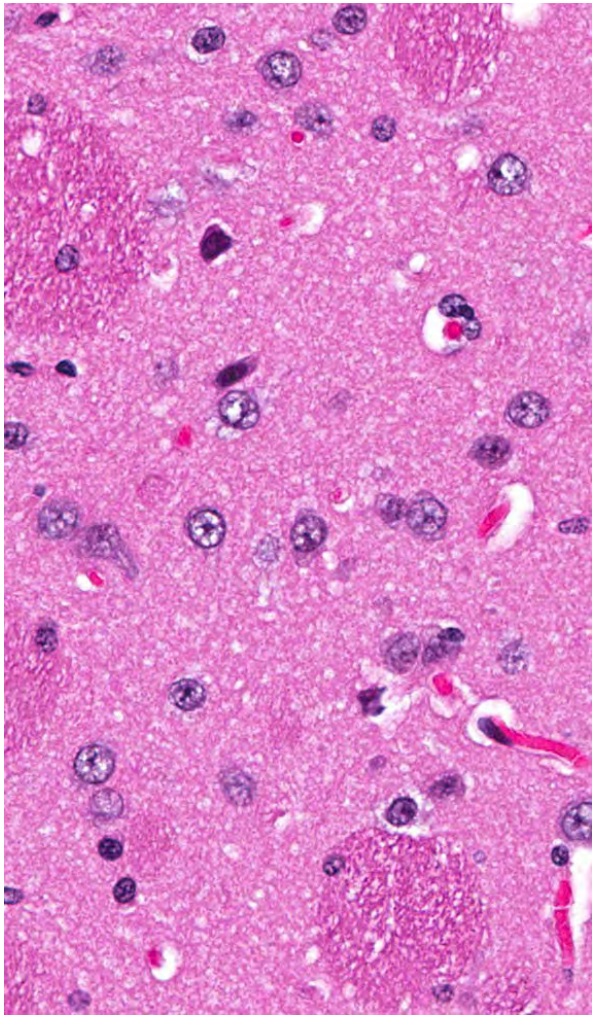


Glial Cell Hyperplasia

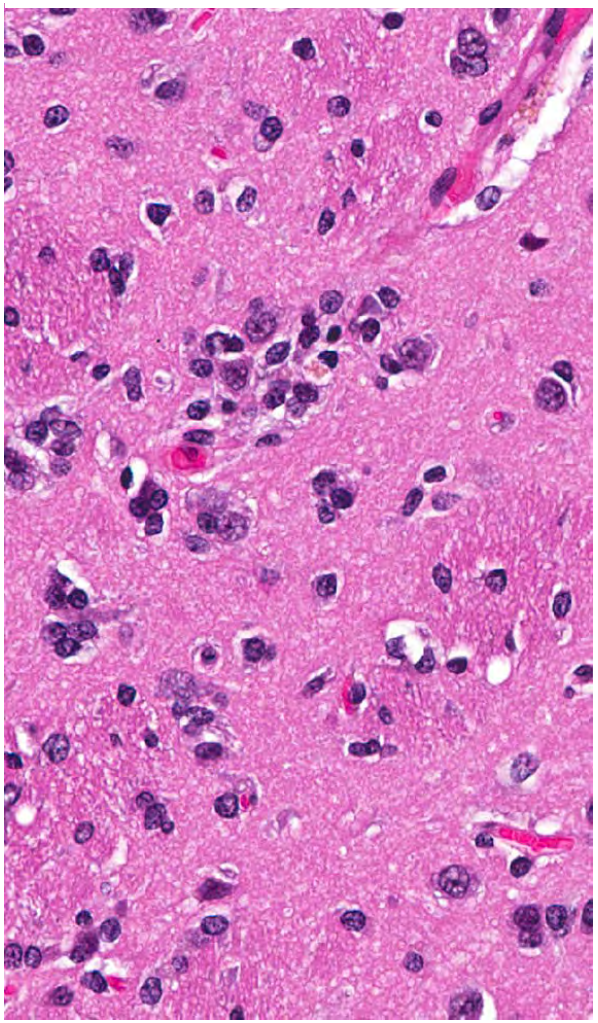


Heart, brain, and kidney lesions

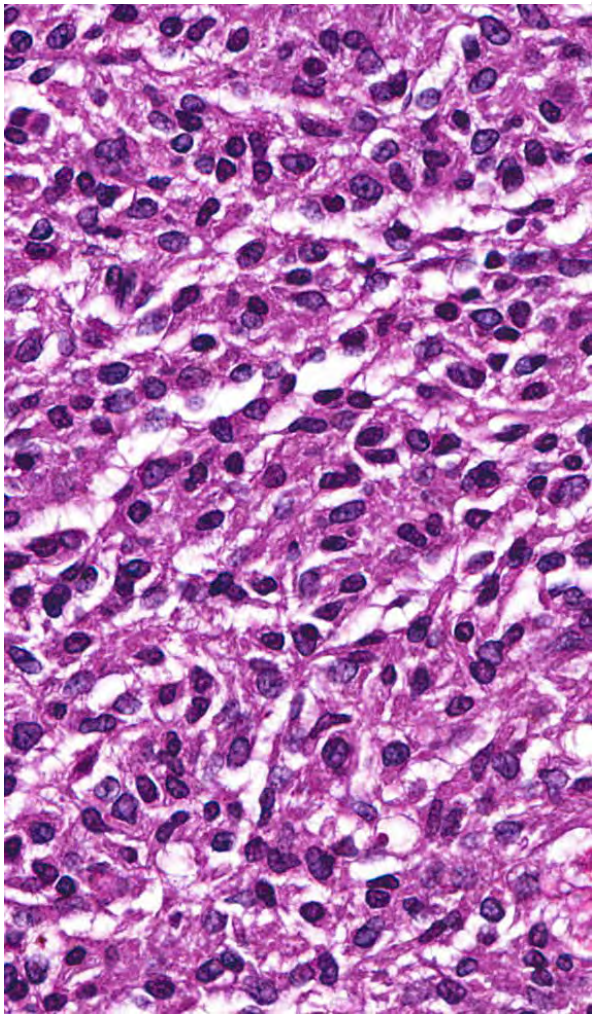
Normal Brain



Glial Cell Hyperplasia



Malignant Glioma



Kidney – Nephropathy, Chronic Progressive and Related Lesions

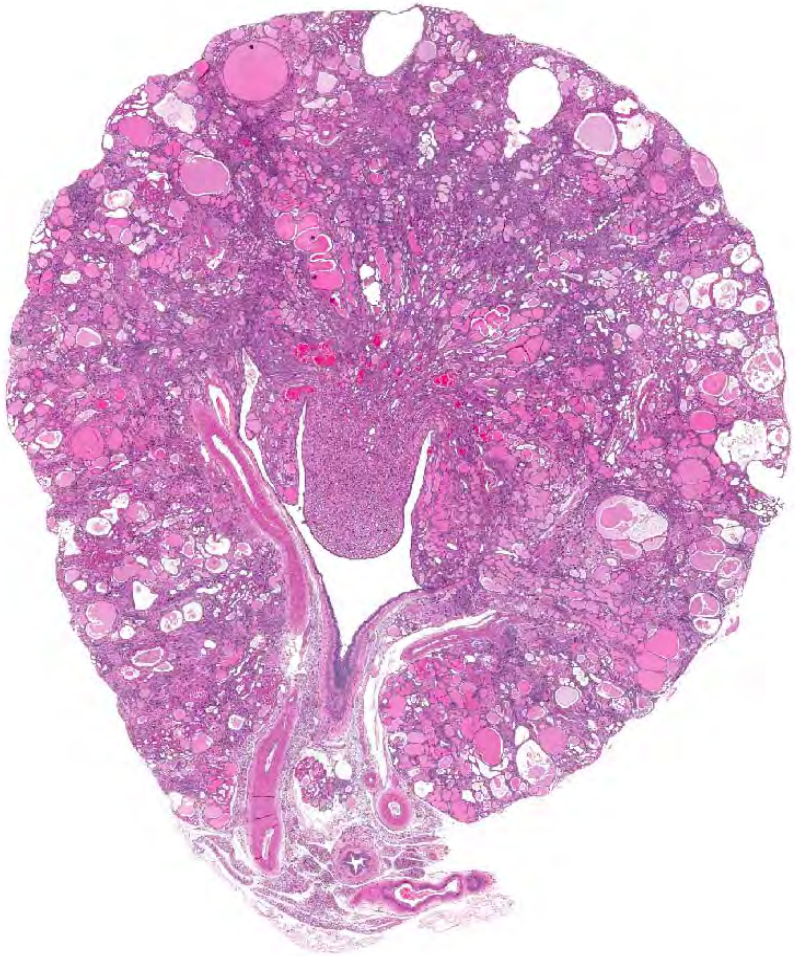
- Considered main reason for decreased survival in control group
- Numerous lesions with decreasing incidences and/or severity were considered to be secondary to chronic progressive nephropathy (see draft NTP Technical Report for rats, Table 29, pg. 113)
  - Parathyroid Gland – Hyperplasia
  - Bone – Fibrous Osteodystrophy
  - Mineral in numerous organs
  - Polyarteritis nodosa (vascular inflammation) and secondary necrosis, degeneration, ulcer, erosion, etc.

Diagnostic Criteria – Chronic Progressive Nephropathy

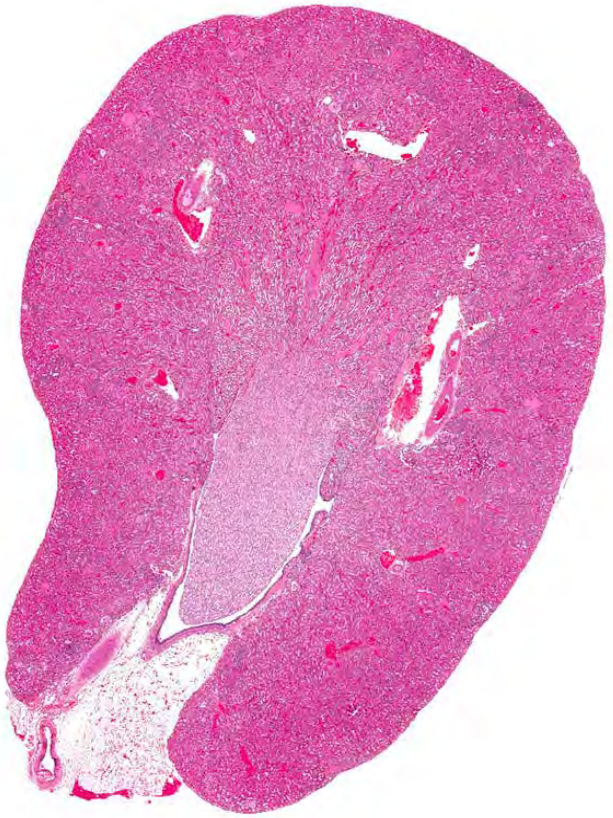
- Tubular epithelial cell regeneration (increased basophilia, cell size, and cell number)
- Basement membrane thickening around tubules
- Mononuclear inflammatory cell infiltrates
- Tubular dilation
- Tubular epithelial cell hyperplasia
- Tubular epithelial cell atrophy
- Protein casts within tubules
- Glomerular changes

Heart, brain, and kidney lesions

Chronic Progressive Nephropathy



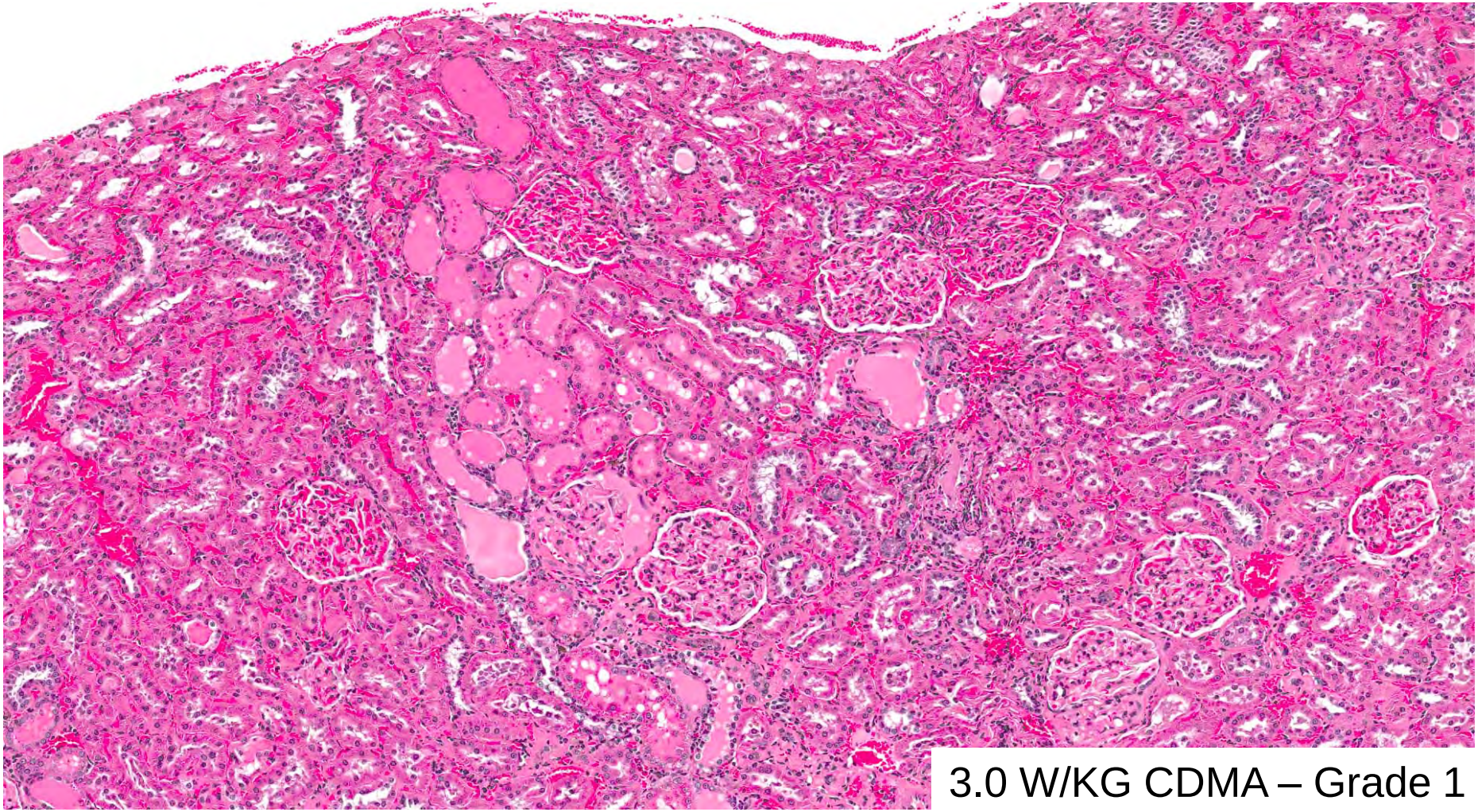
Control – Grade 4



3.0 W/KG CDMA – Grade 1

Heart, brain, and kidney lesions

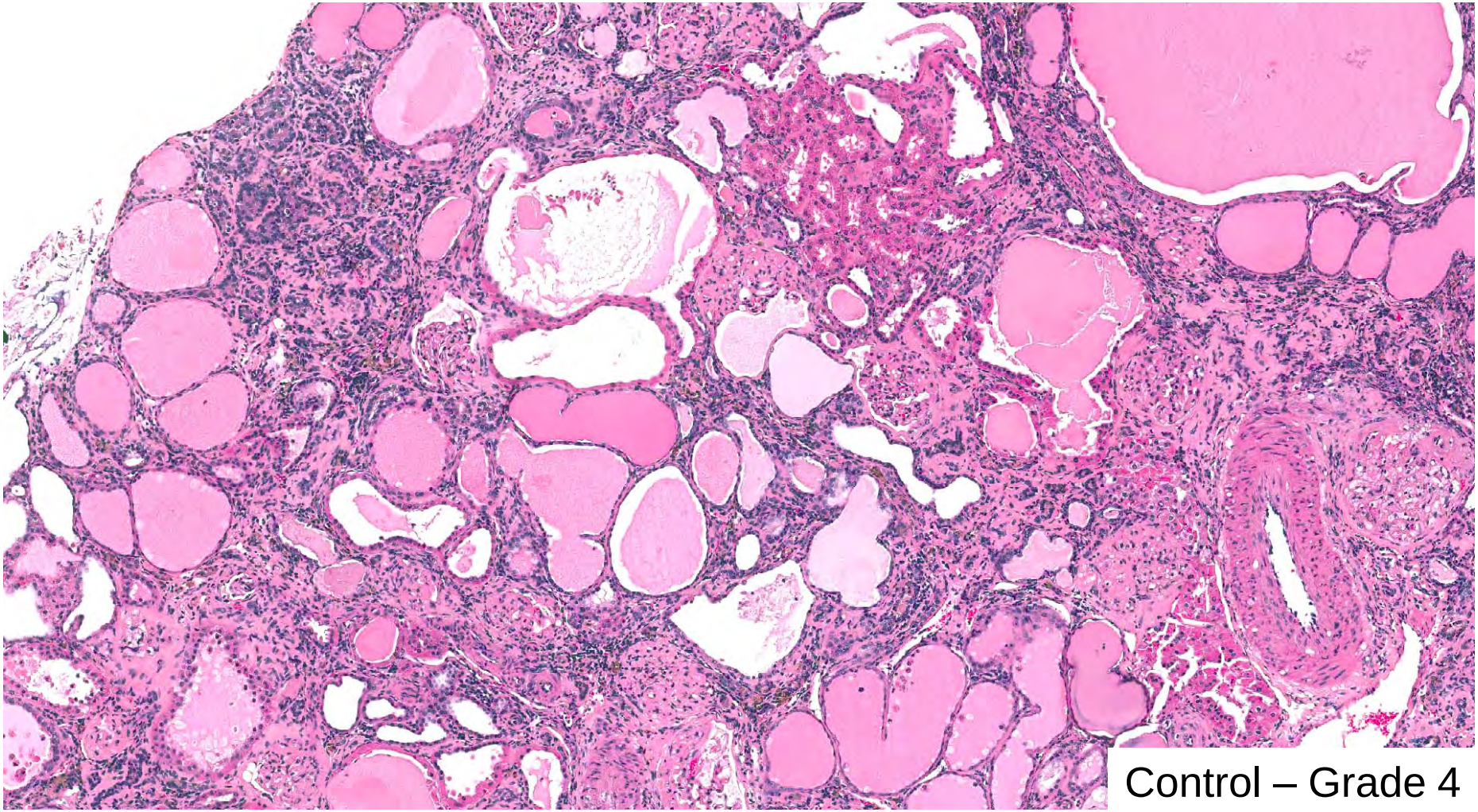
Chronic Progressive Nephropathy



3.0 W/KG CDMA – Grade 1

Heart, brain, and kidney lesions

Chronic Progressive Nephropathy



Control – Grade 4

Thank you