American Association of Neuropathologists

Diagnostic Slide Session 2024 – Case #1
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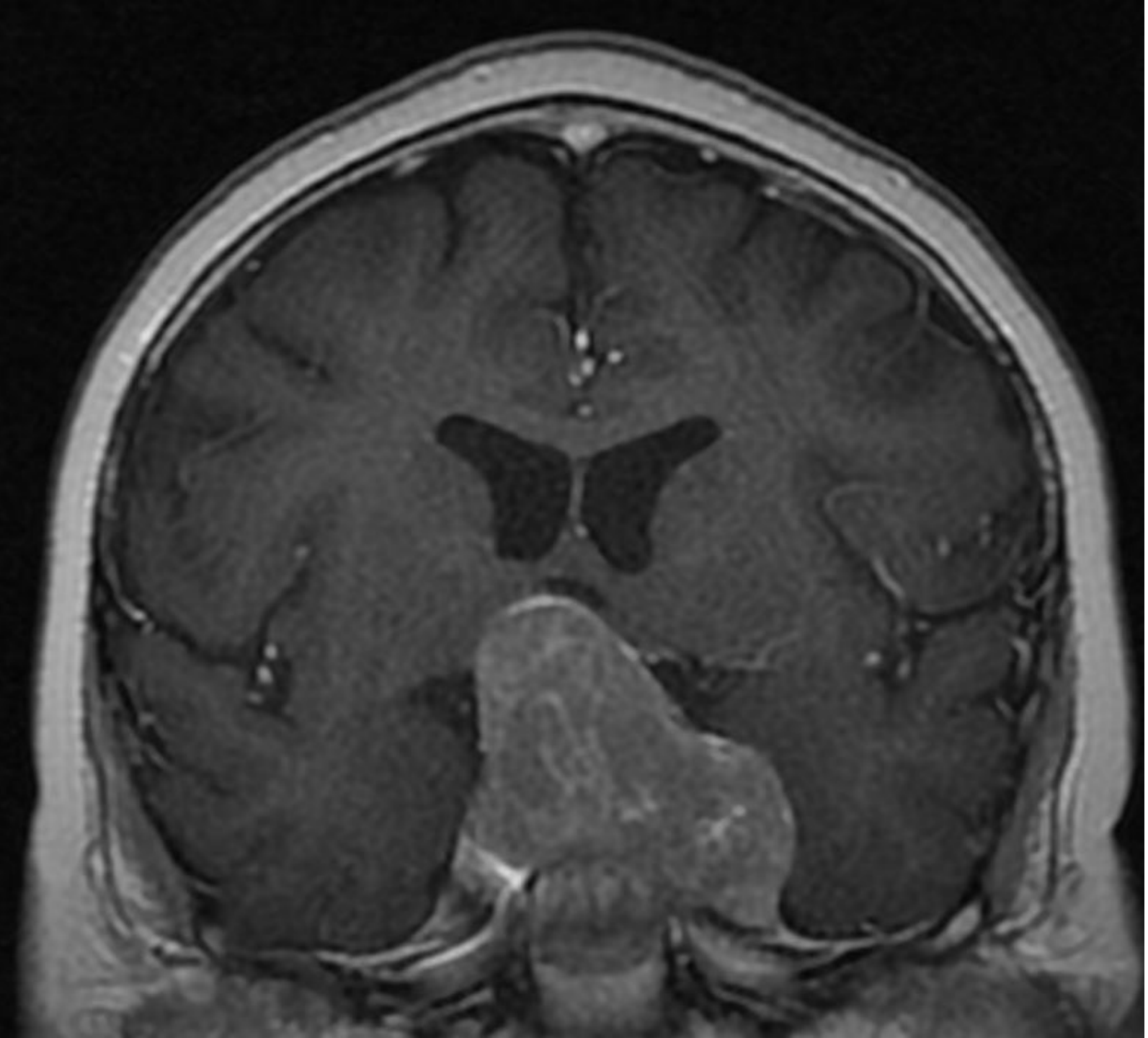
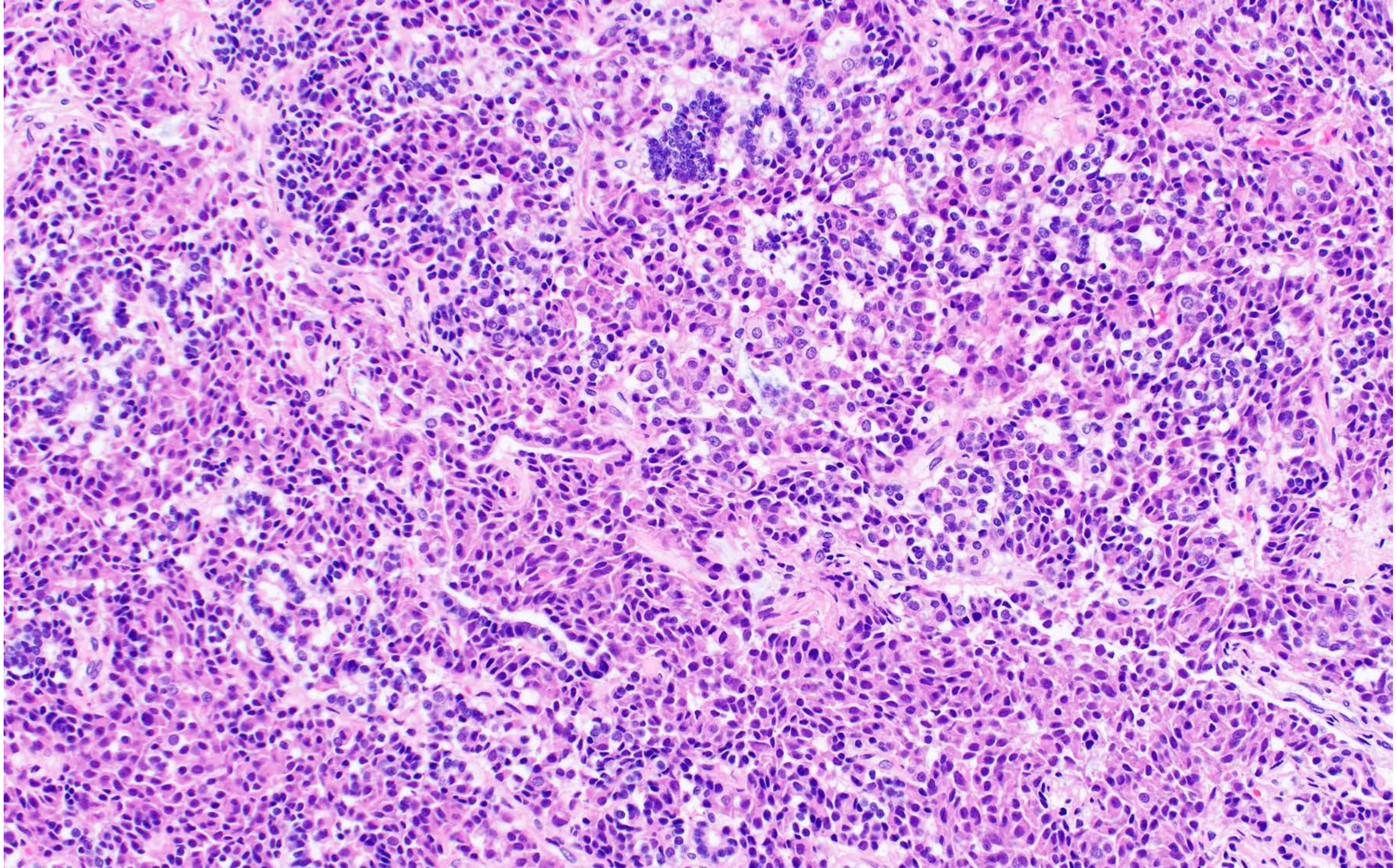
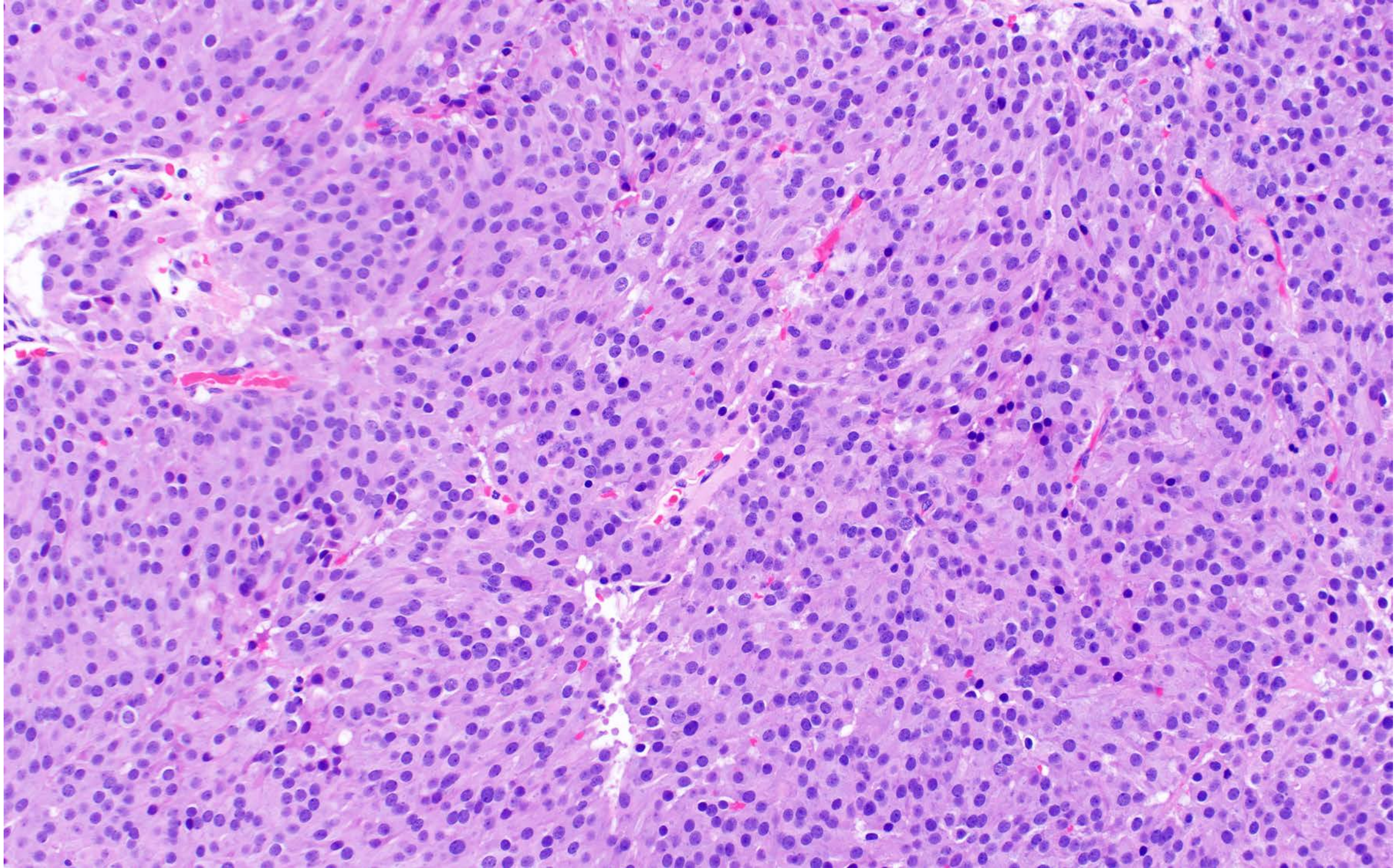


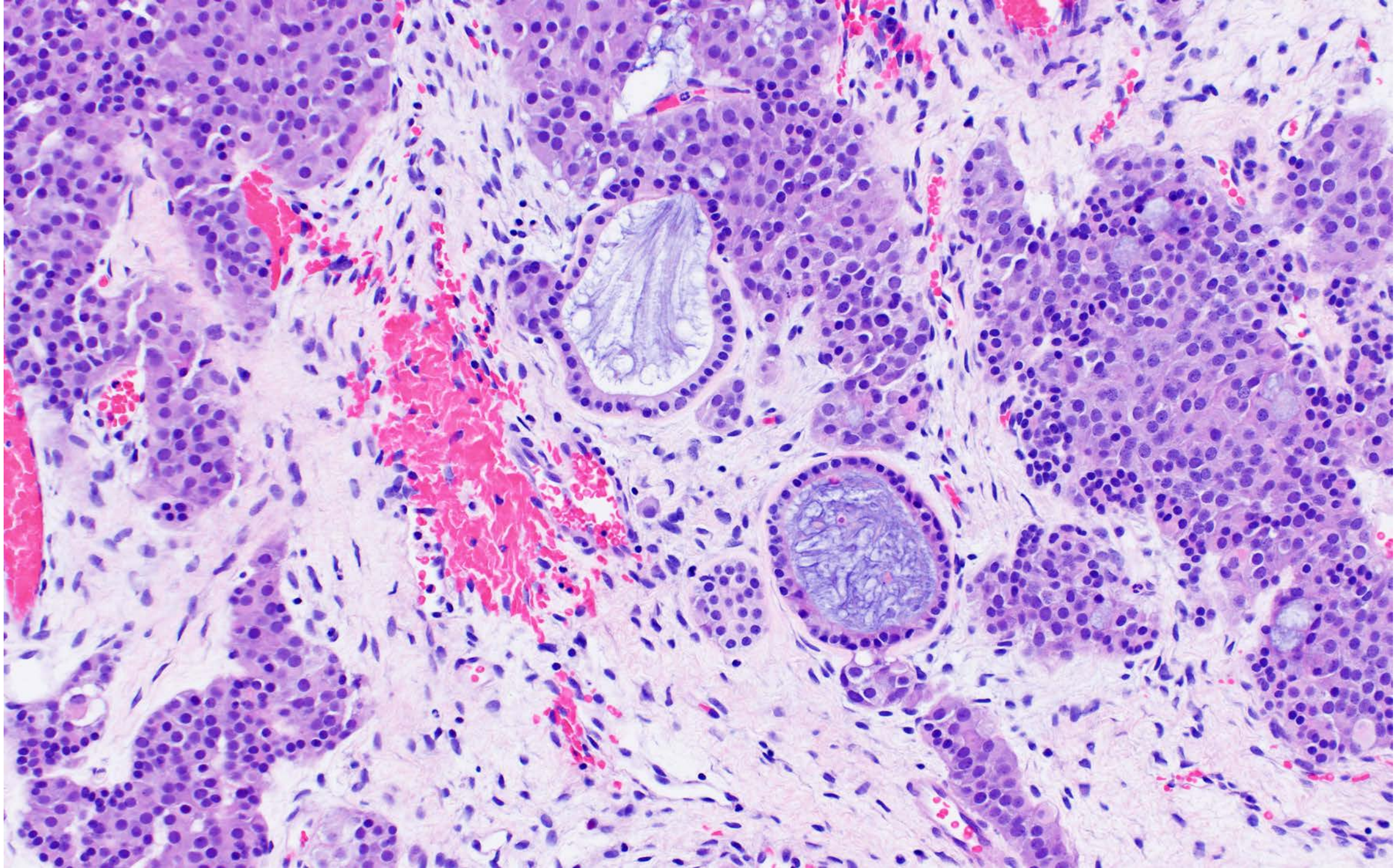
2-year-old male

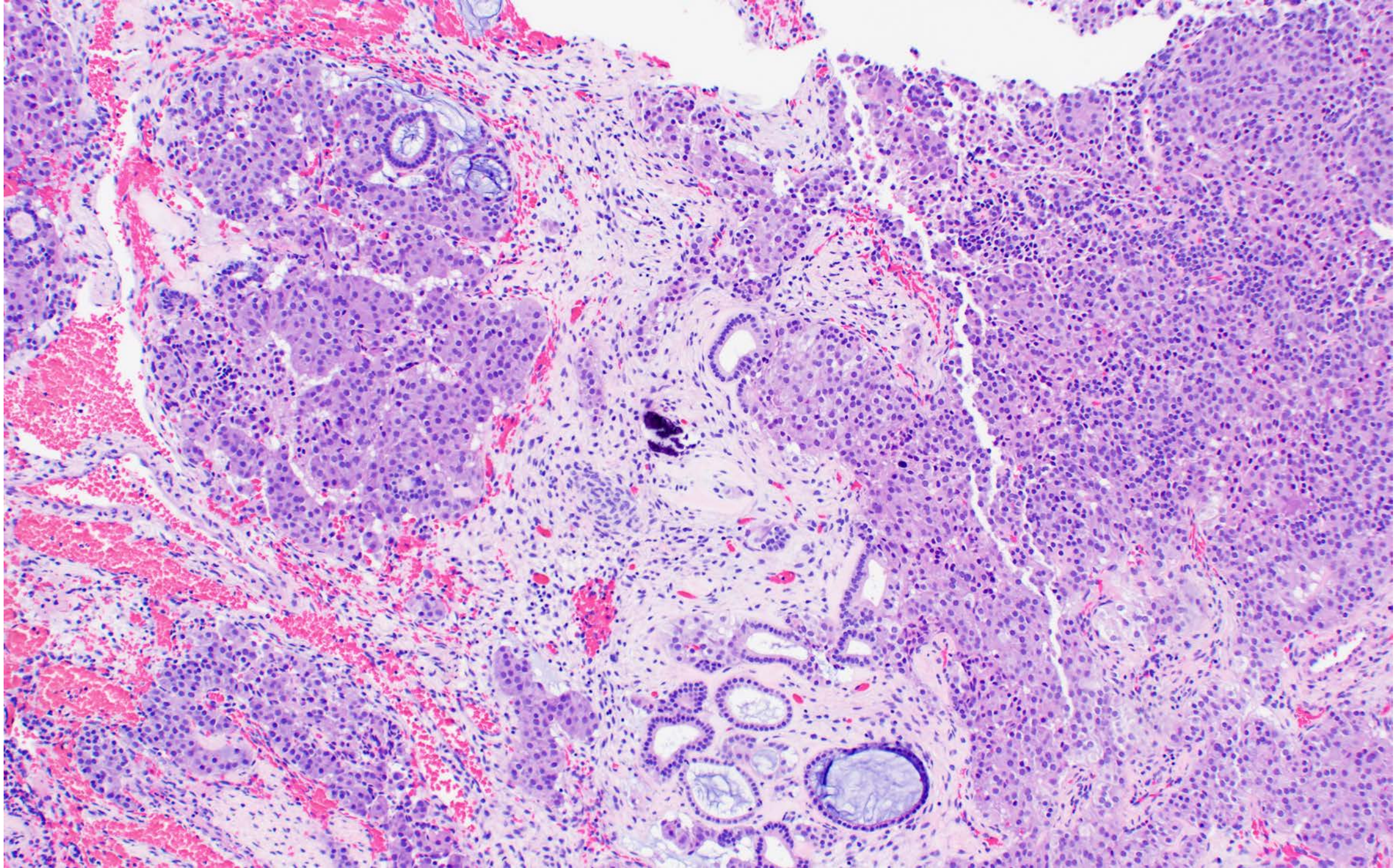
normal at birth, subsequently presented with weight gain

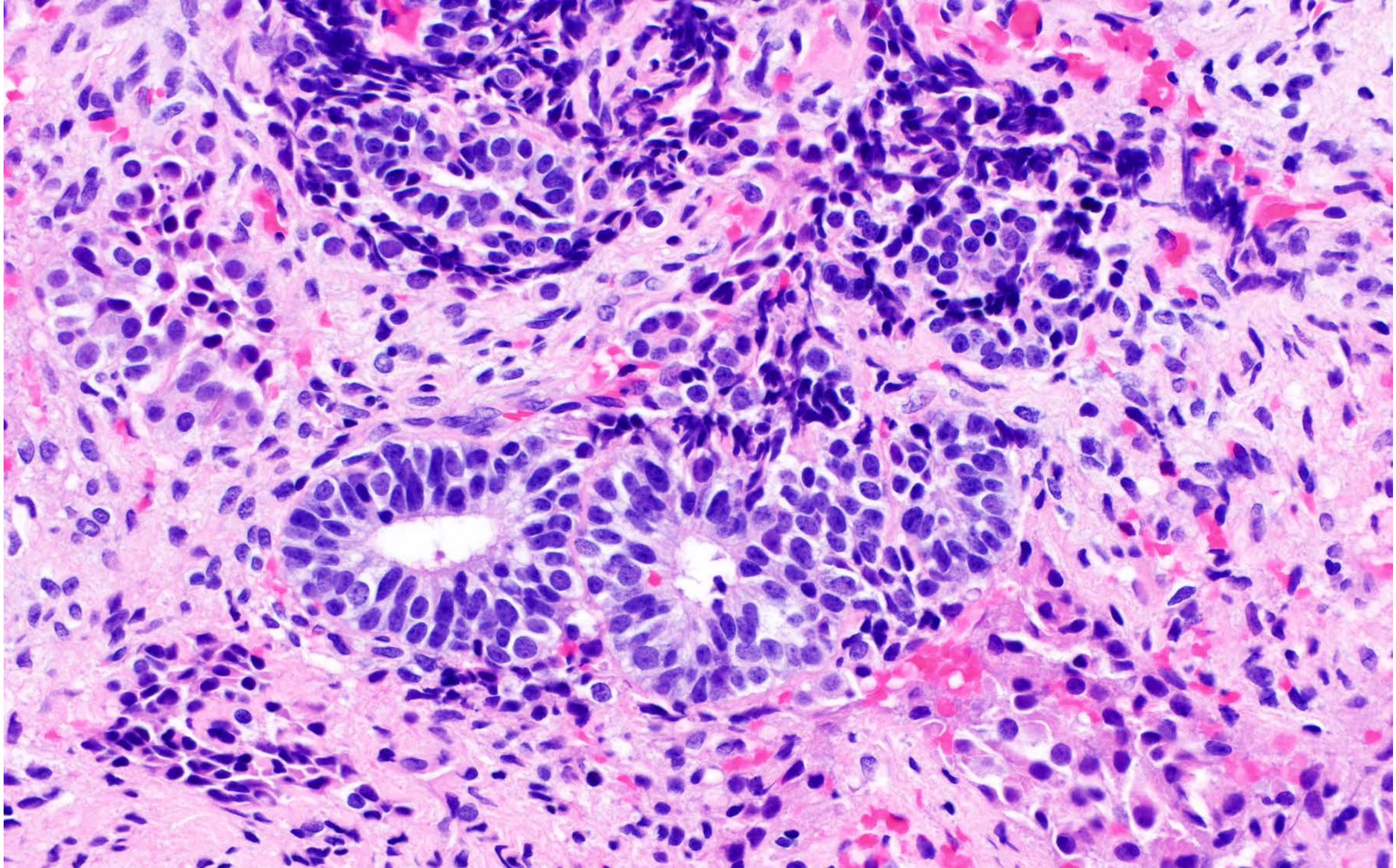
found to have a 3.9 cm sellar/suprasellar mass with bilateral cavernous sinus invasion (L>R)

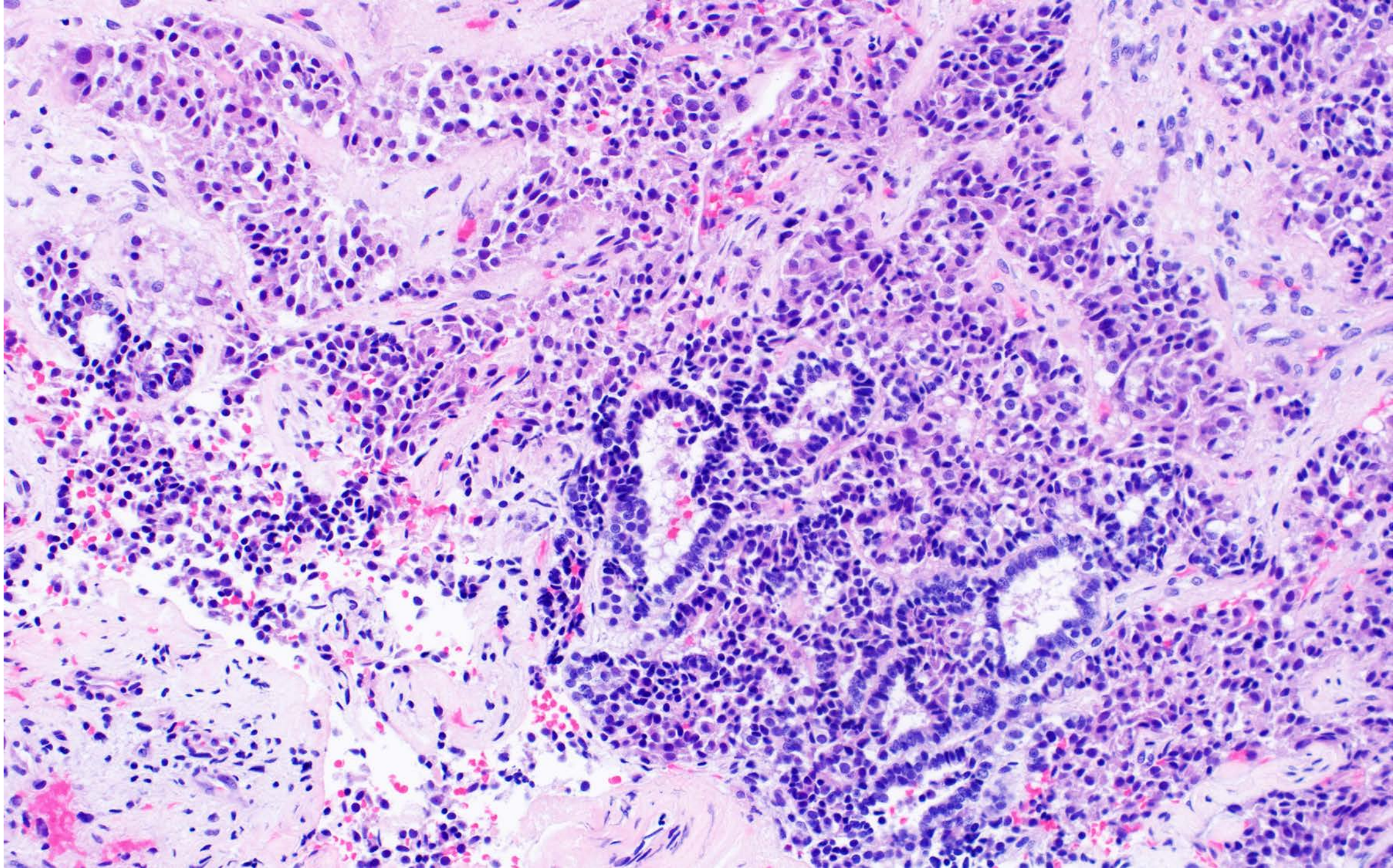


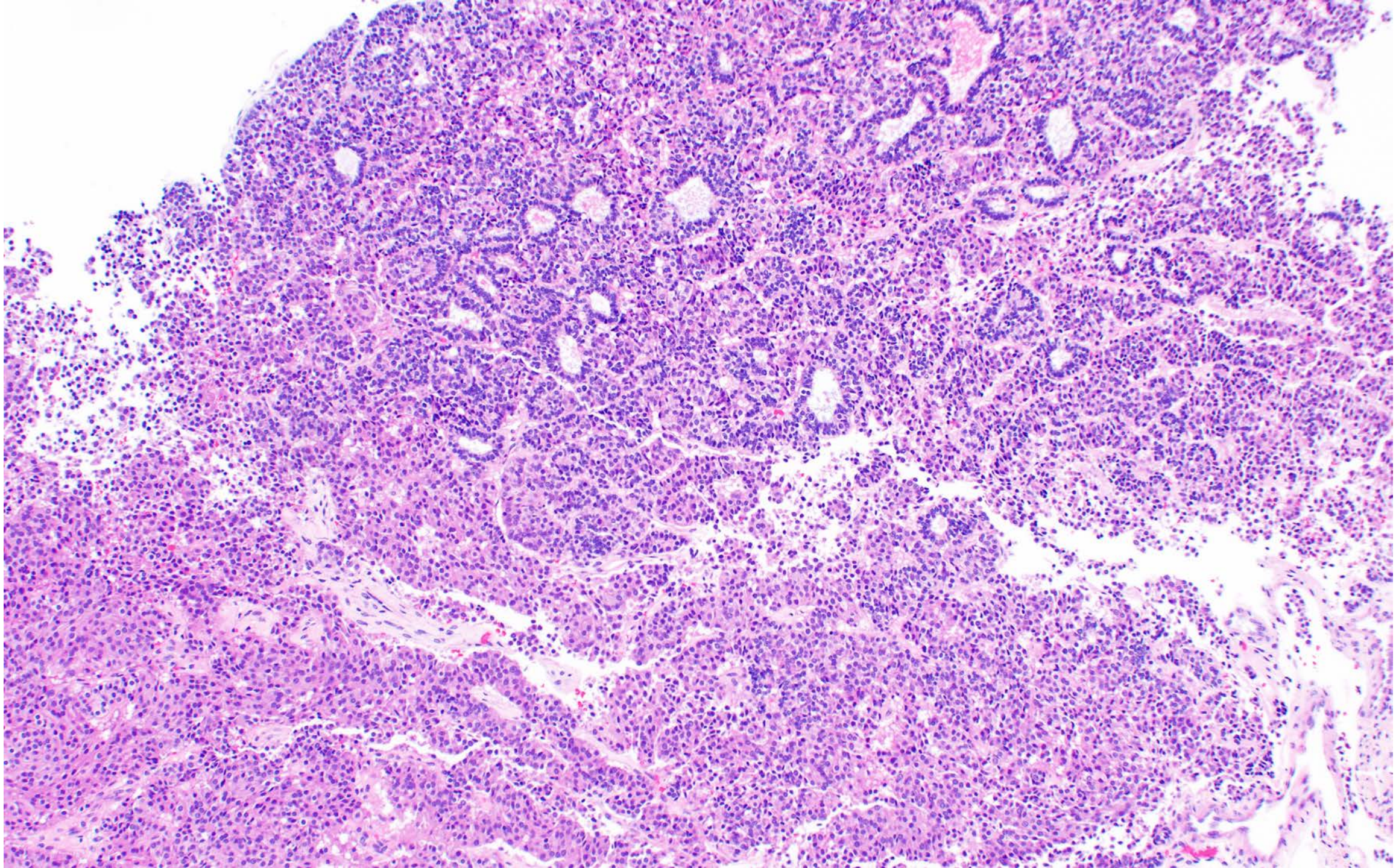


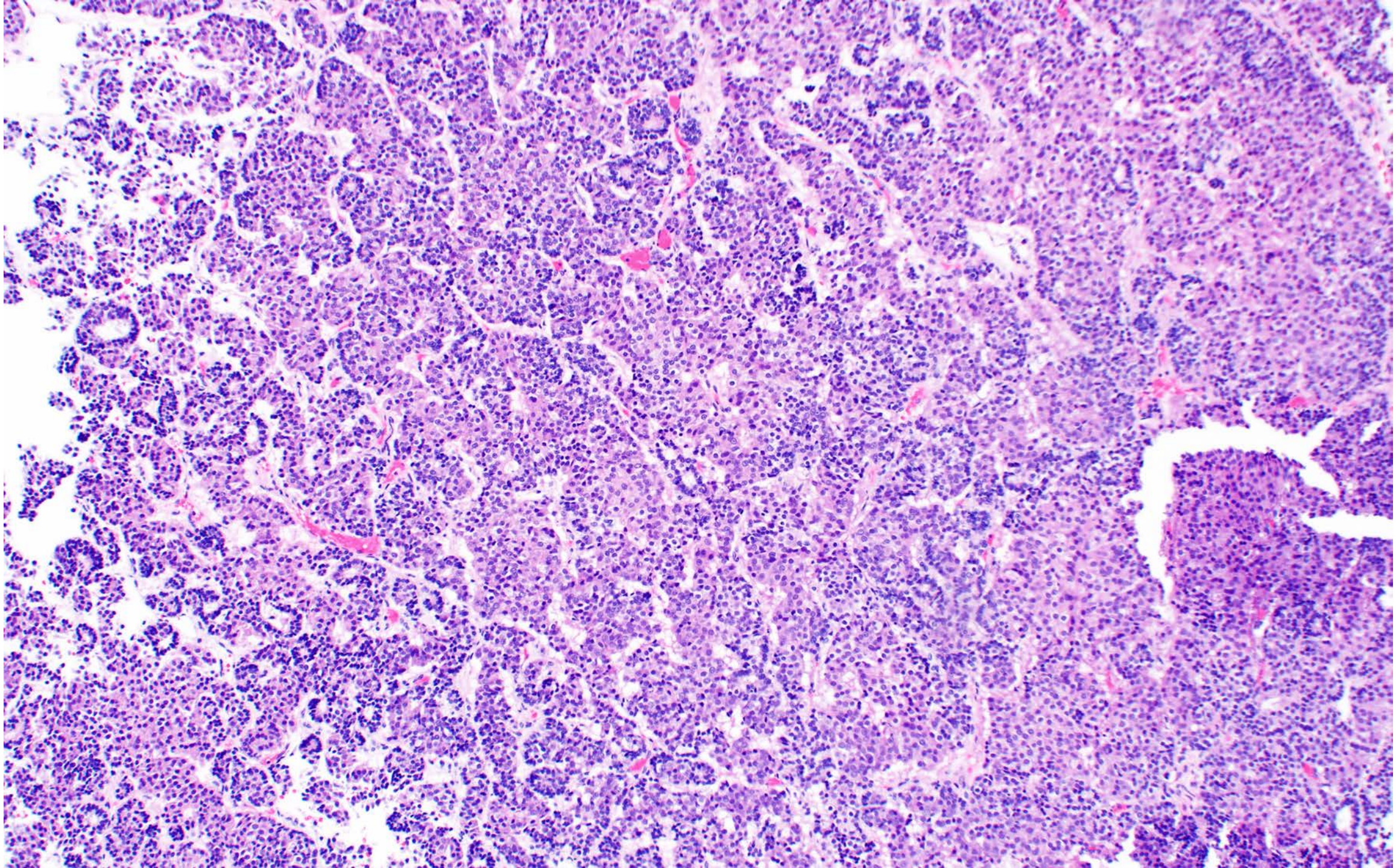


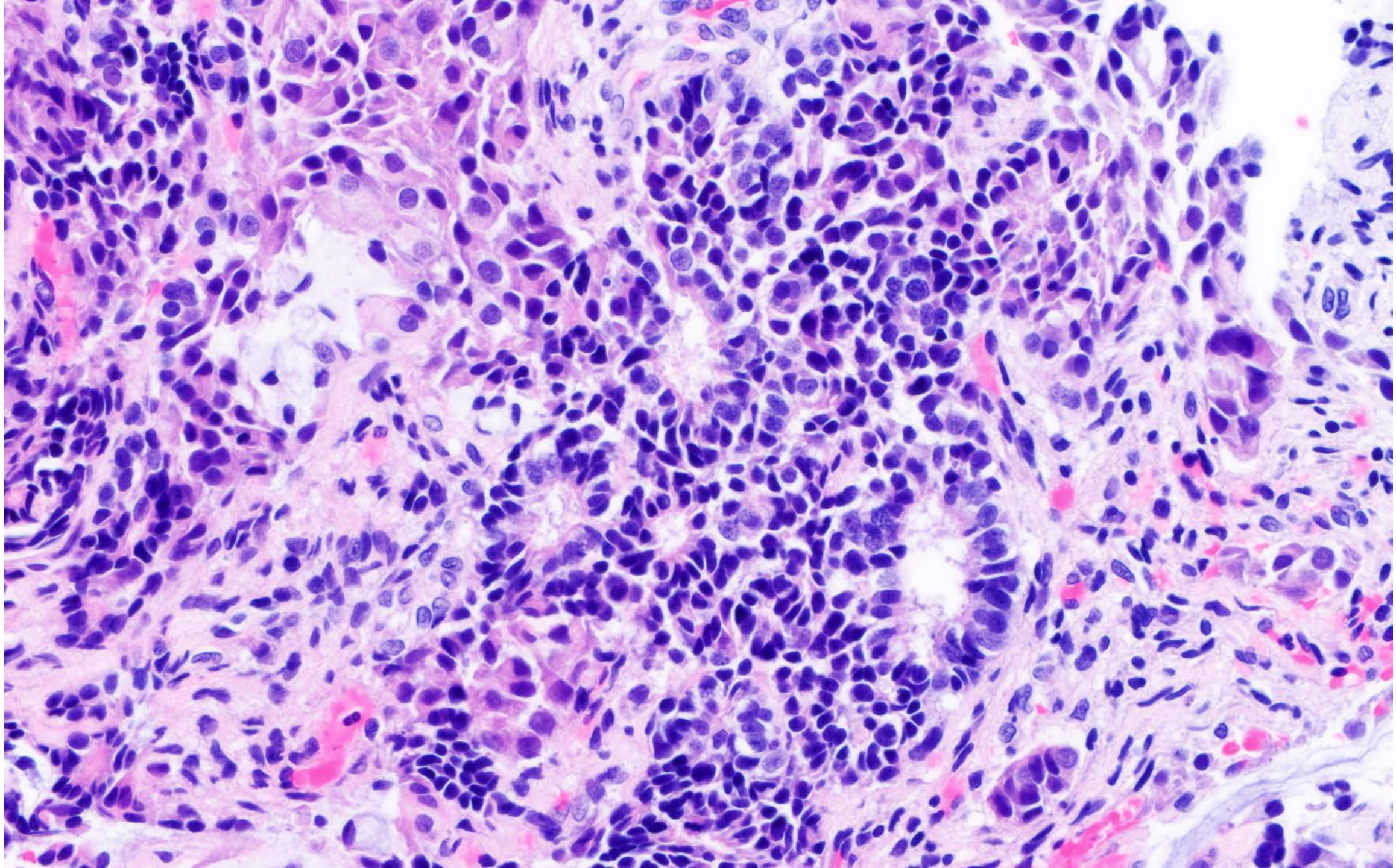


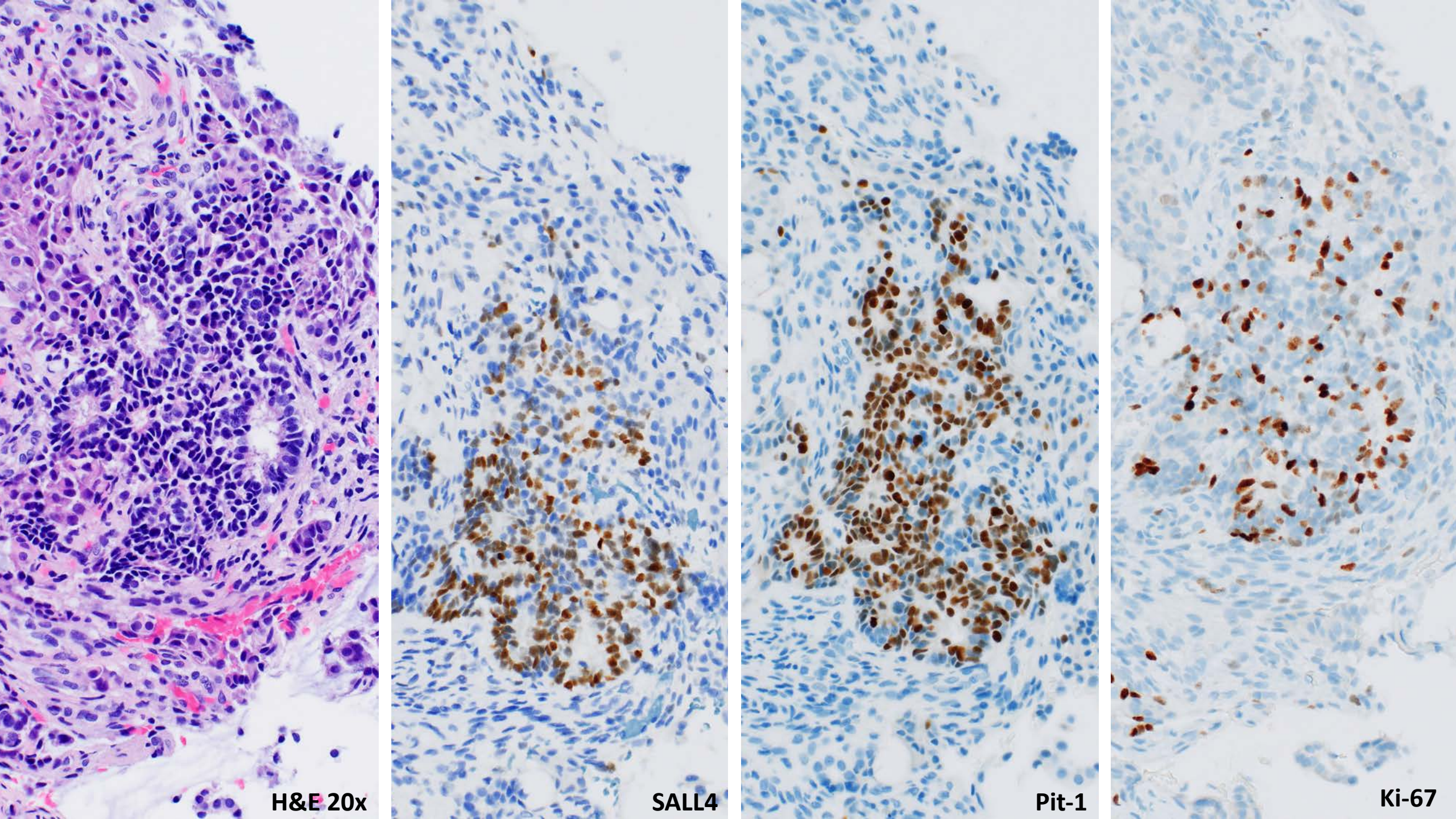








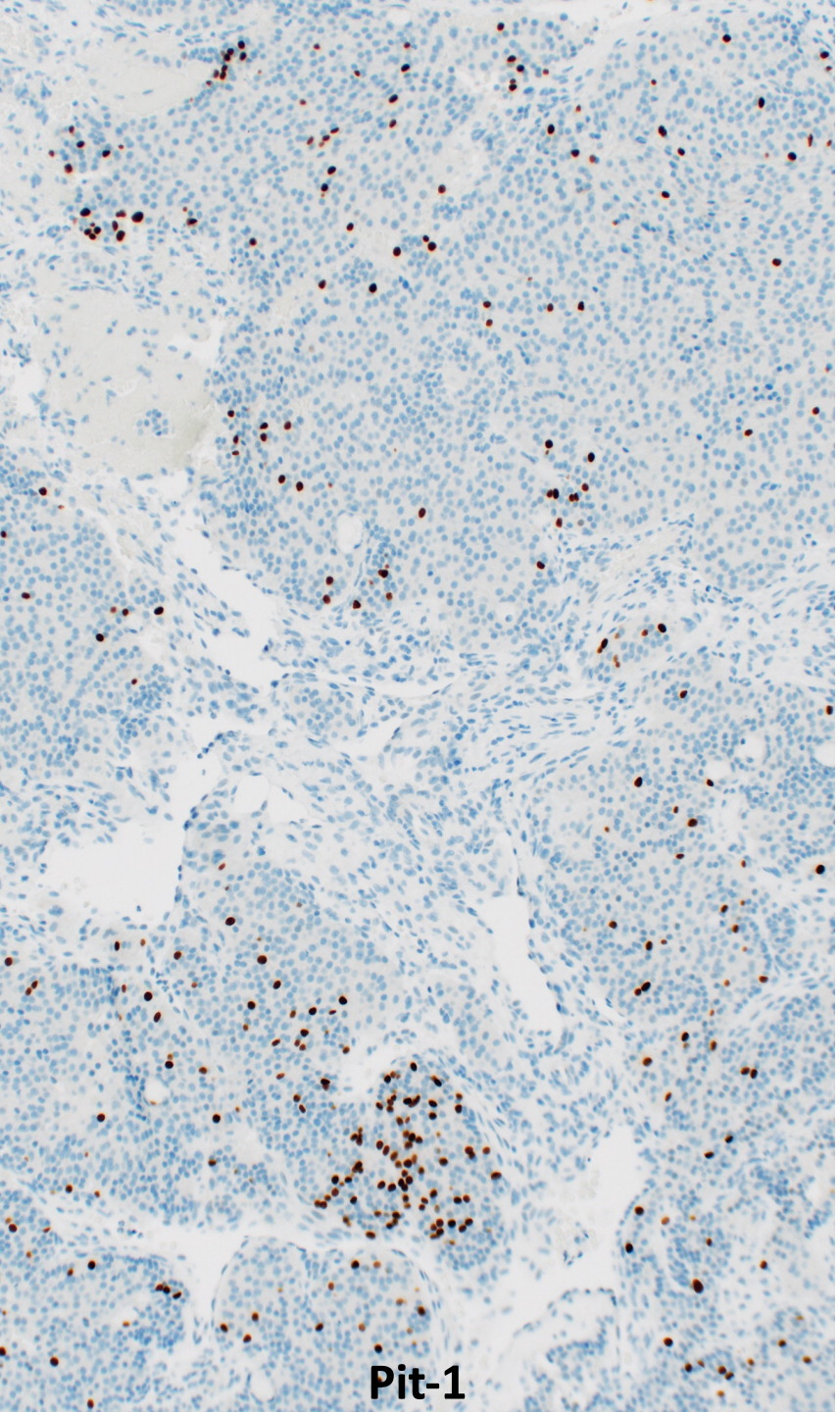


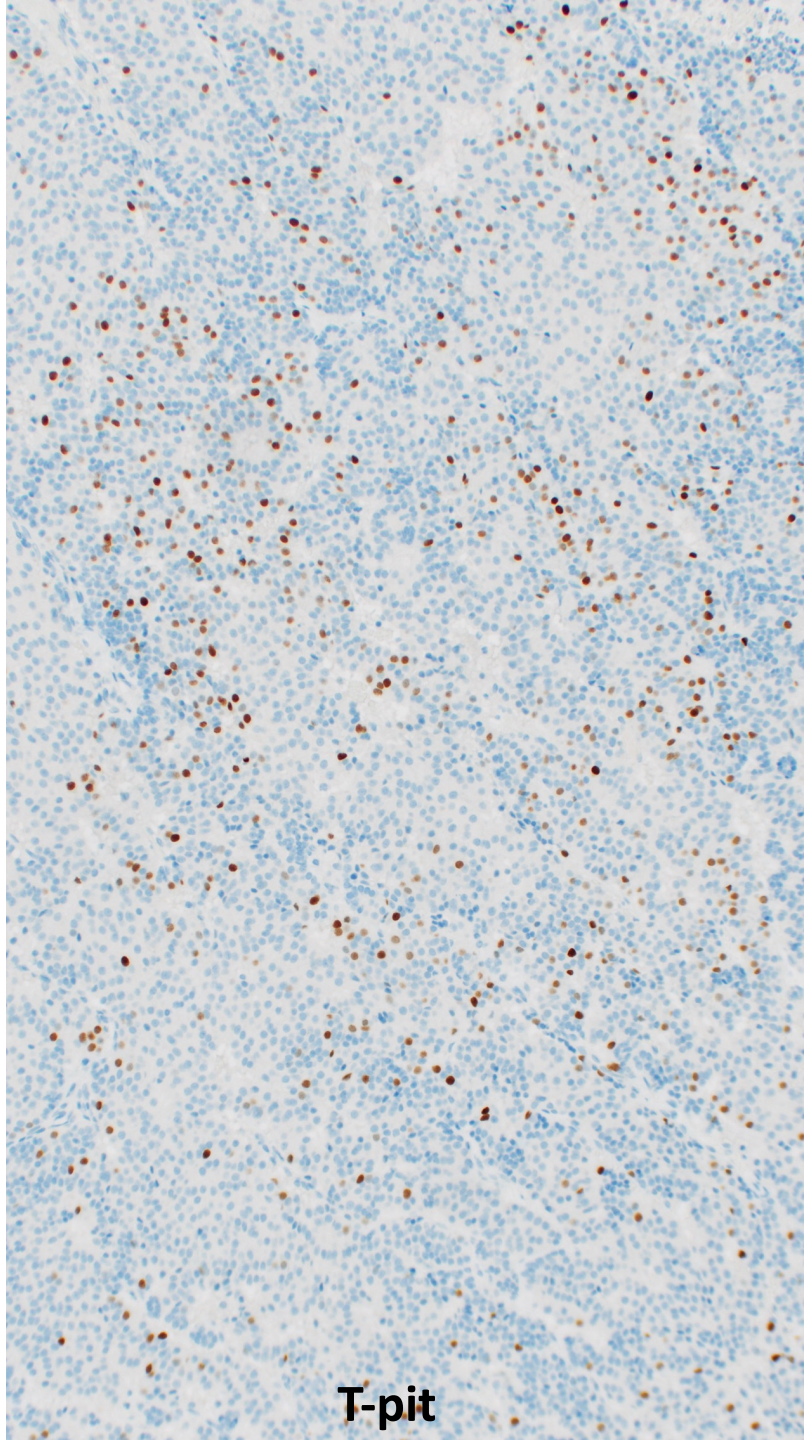

H&E 20x
SALL4
Pit-1
Ki-67

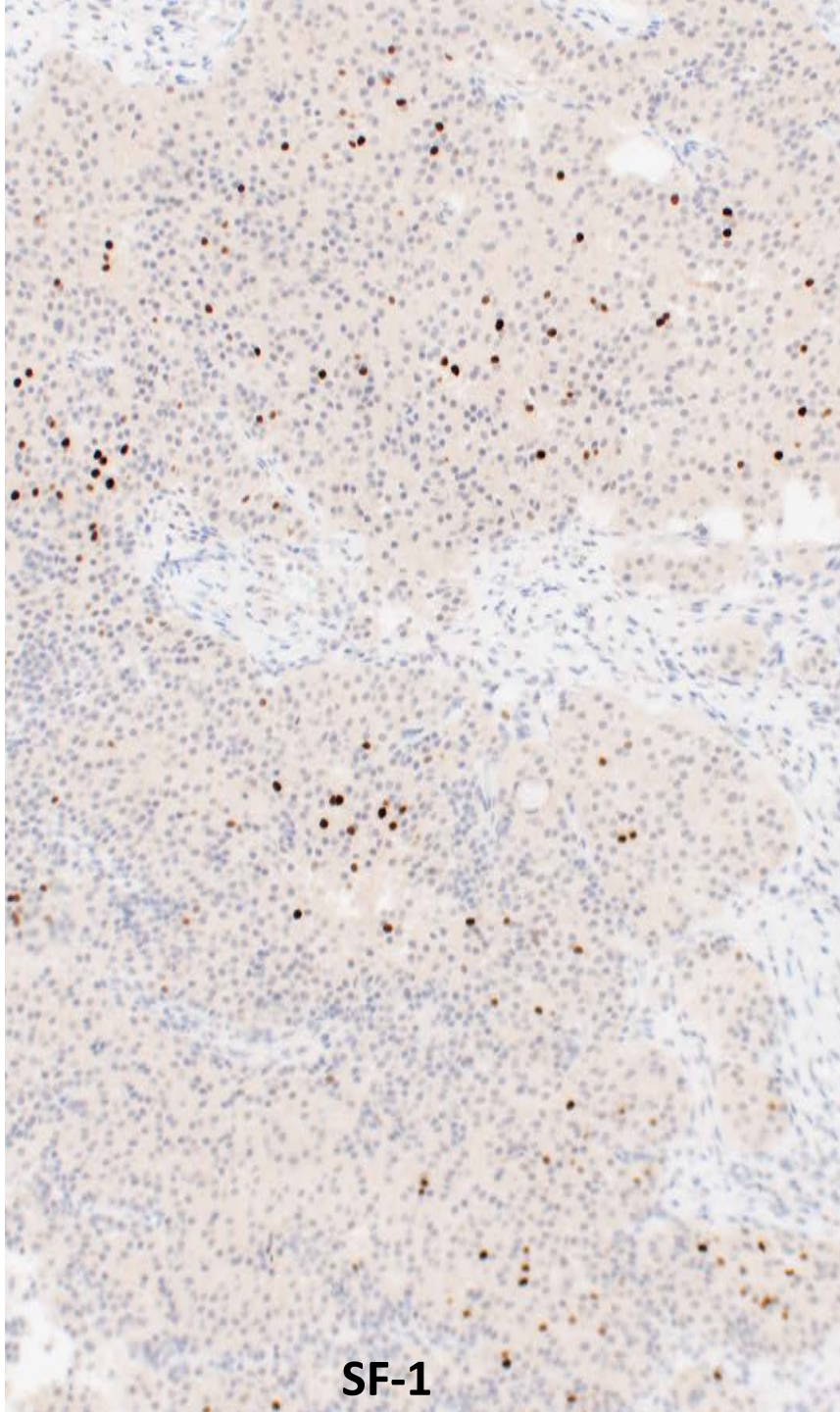
Case Discussion

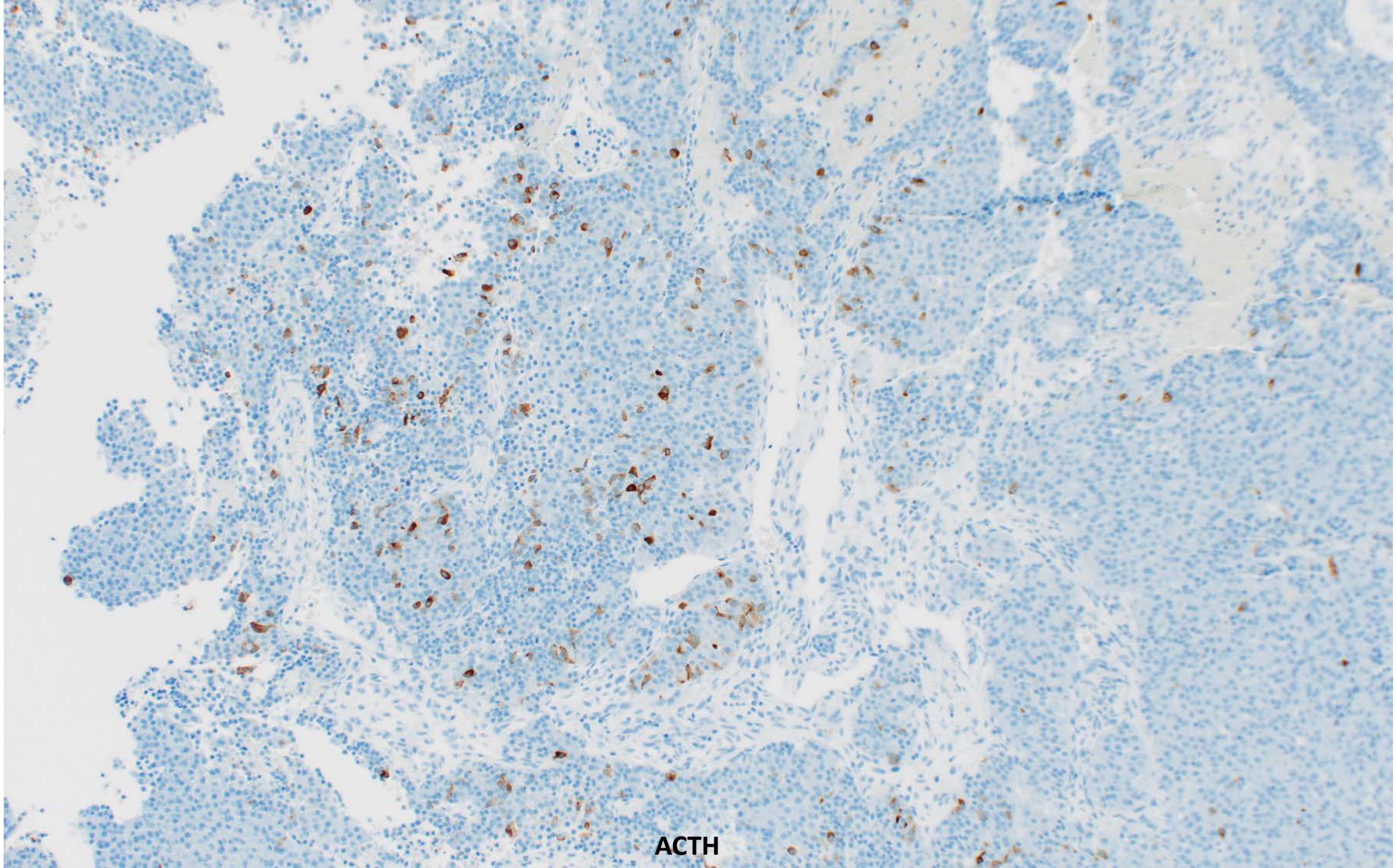
Differential Diagnosis?

Diagnostic Studies?


Pit-1


T-pit


SF-1



ACTH

Tumor and germline sequencing analysis demonstrated:

Germline *DICER1* frameshift mutation

Somatic *DICER1* hotspot mutation in the ribonuclease III domain

Germline loss of function mutations in *DICER1* cause a rare autosomal dominant tumor predisposition syndrome (OMIM #601200)

SINGLE NUCLEOTIDE VARIANTS AND INDELS

Alteration	HGVS Nomenclature	Allele Frequency
DICER1 D1810Y	NM_177438.2: c.5428G>T; p.Asp1810Tyr	45% WES, 68% RNA
DICER1 frame-shift indel	NM_177438.2: c.2022del; p.Leu675PhefsTer10	42% WES, 17% RNA

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ORIGINAL PAPER

Pituitary blastoma: a pathognomonic feature of germ-line *DICER1* mutations

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Abstract Individuals harboring germ-line *DICER1* mutations are predisposed to a rare cancer syndrome, the *DICER1* Syndrome or pleuropulmonary blastoma-familial tumor and dysplasia syndrome [online Mendelian inheritance in man (OMIM) #601200]. In addition, specific somatic mutations in the DICER1 RNase III catalytic domain have been identified in several *DICER1*-associated tumor types. Pituitary blastoma (PitB) was identified as a distinct entity in 2008, and is a very rare, potentially lethal early childhood tumor of the pituitary gland. Since the discovery by our team of an inherited mutation in *DICER1* in a child with PitB in 2011, we have identified 12 additional PitB cases. We aimed to determine the contribution of germ-line and somatic *DICER1* mutations to PitB. We hypothesized that PitB is a pathognomonic feature of a germ-line *DICER1* mutation and that each PitB will harbor a second somatic mutation in *DICER1*. Lymphocyte or saliva DNA samples ascertained from ten infants with PitB were screened and nine were found to harbor a heterozygous germ-line *DICER1* mutation. We identified additional *DICER1* mutations in nine of ten tested PitB tumor samples, eight of which were confirmed to be somatic in origin. Seven of these mutations occurred within the RNase IIIb catalytic domain, a domain essential to the generation of 5p miRNAs from the 5′ arm of miRNA-precursors. Germ-line *DICER1* mutations are

This paper is dedicated to Bernd W. Scheithauer, MD, with whom several of the co-authors have trained and/or collaborated. Bernd was a world-renowned neuropathologist with special expertise in pituitary disease. With his colleagues, Bernd described pituitary blastoma (PitB) in 2008 and he was an early participant in the work reported here. Just before his untimely death, he was thrilled to learn that several additional PitB cases had been accessioned and more so that *DICER1* mutations explain PitB and its association with other childhood blastomas in this familial tumor predisposition syndrome.

Electronic supplementary material The online version of this article (doi:10.1007/s00401-014-1285-z) contains supplementary material, which is available to authorized users.

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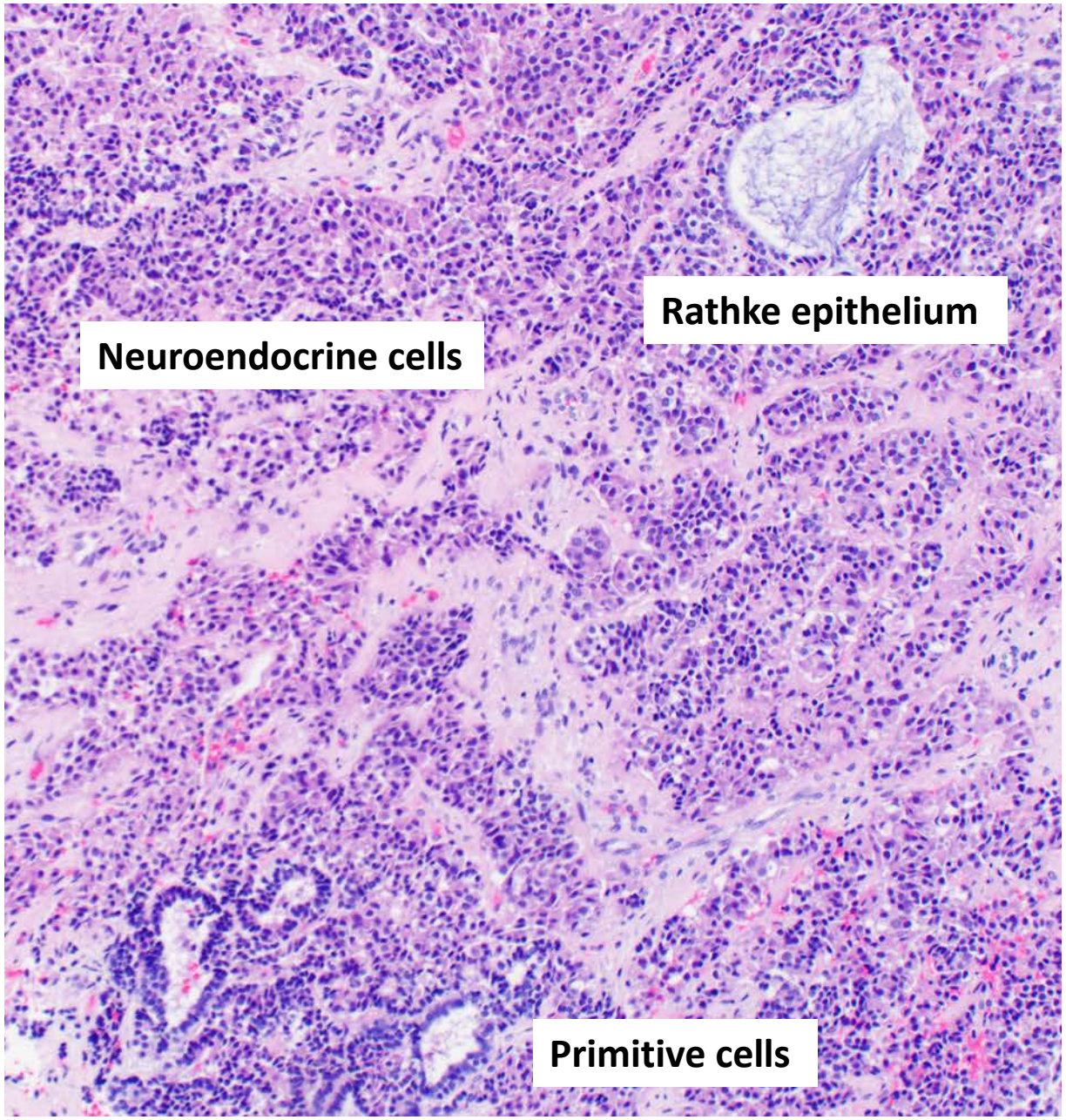
Pituitary blastoma with *DICER1* mutation



- Sellar region neoplasm composed of primitive cells, neuroendocrine cells, and Rathke epithelium
- Exceptionally rare tumor
- Usually occurs in children less than 2 years of age
- Cushing syndrome is one of the most common presentations
- Associated with germline and somatic mutations in *DICER1*, which encodes a microRNA processing enzyme
- Patients may present with or subsequently develop other *DICER1* related tumors

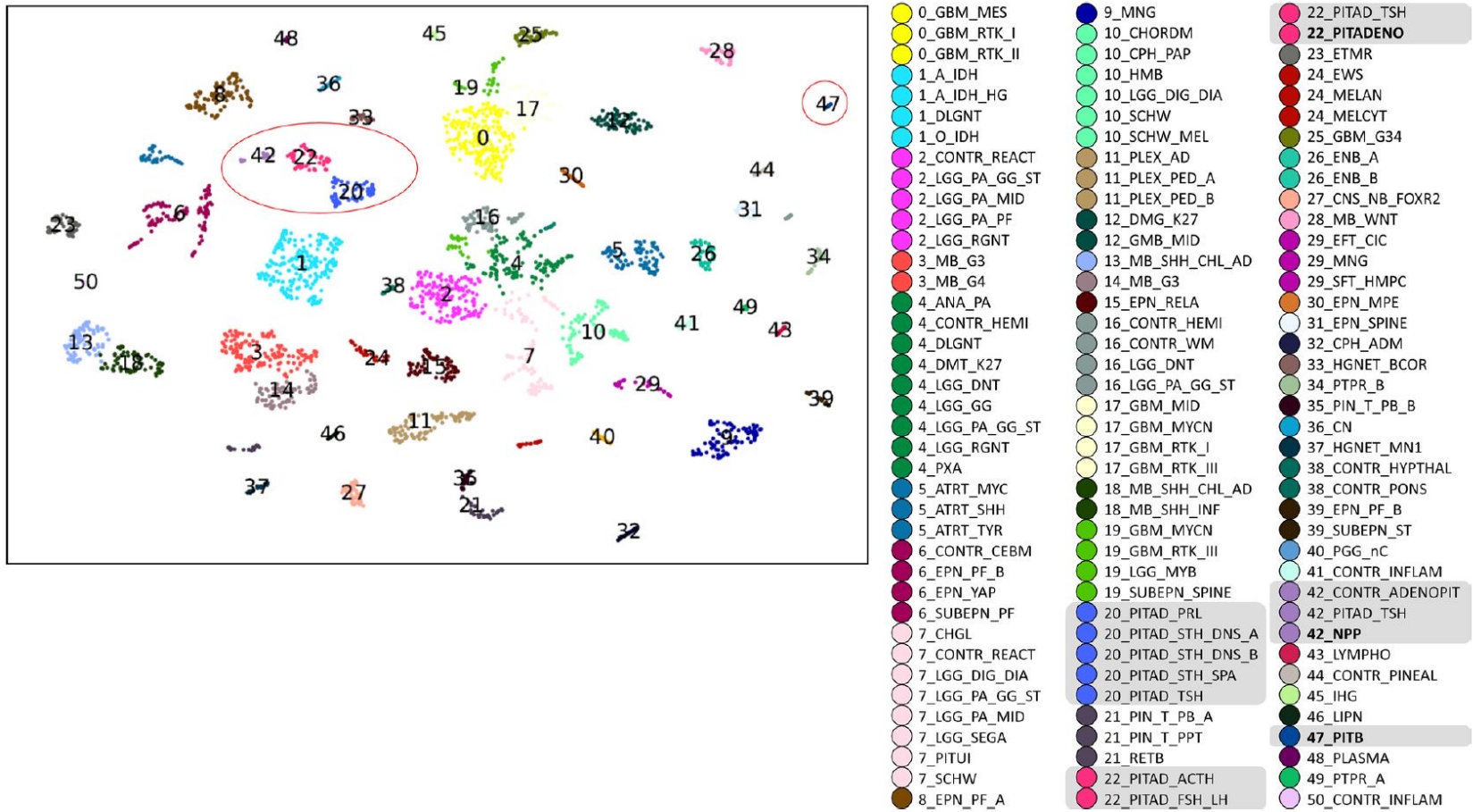


Fig. 6 Methylation-based clustering of PitB with a cohort of CNS tumors and control tissues. Uniform Manifold Approximation and Projection (UMAP) visualization of methylation data using 50 k most variable CpG loci and unsupervised clustering (see methods for Louvain clustering); data were obtained from a previously published large-scale study of CNS tumors ($n=2801$) [8] or were generated in-house ($n=17$). Each point represents one sample and is color coded based on the tumor pathological type or control tissues. Pituitary samples are circled on the UMAP and highlighted on the legend. The legend names are in Cluster_CellType format. There is a total of 51 clusters. PitB samples form a distinct cluster (cluster 47) separate from pituitary adenoma samples (clusters 20, 22, 42)

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