Case of the Month August 2020

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Case 1

- 73/F, Diabetic, Hypertensive presented with Left breast lump ~ 1 week

- O/E: Left Breast lump noted at 9 o'clock measuring 3X2 cm. No axillary node palpable. Rt Breast : Nodularity in retroareolar area

- Mammogram : Revealed lesion in lower inner quadrant of left breast

- Tru Cut Biopsy (Review): Features suggestive of Neuroendocrine tumor, Grade II (90%) along with focus of invasive breast carcinoma , GradeII (10%)

- FNAC : Left axillary Lymph Node: Negative for malignant cells

- PET CT : No distant metastasis

- Patient underwent left modified radical mastectomy with axillary level I and II dissection

- On gross examination, single tumor measuring 3 x 2.5 x 2 cm was noted in the inner quadrant of the left breast

Histopathology Report - MICROSCOPY

. Sections revealed invasive neoplasm arranged in nests and jigsaw pattern, composed of monomorphic tumor cells with eosinophilic cytoplasm, ovoid nuclei and prominent nucleoli

. Ductal Carcinoma In Situ(DCIS): Present; solid and cribriform, intermediate grade

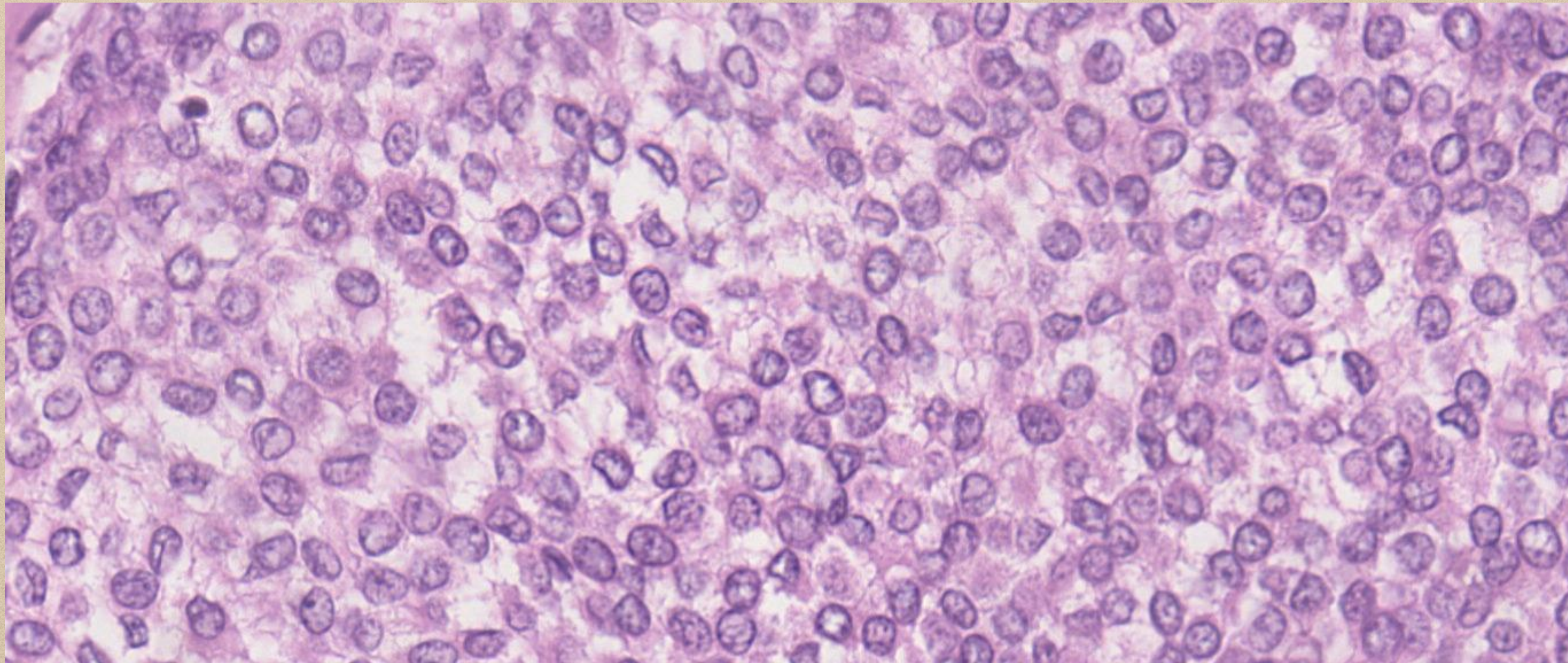. 14 axillary lymph nodes were isolated, all were free of tumor (0/14)

- On IHC, the tumor cells showed Diffuse Positivity for Synaptophysin

- Ki67 Proliferation Index - 10%

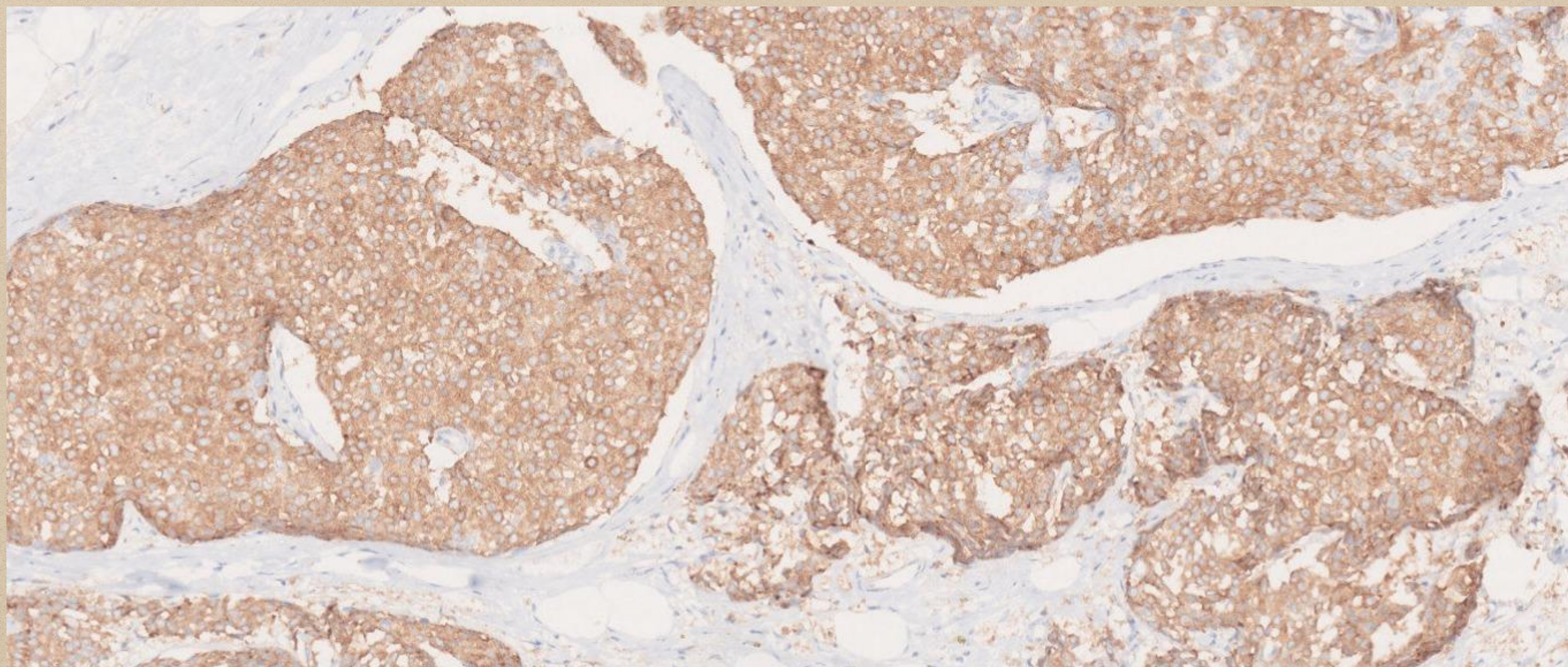- Negative immunoexpression of lining myoepithelial cells by p63
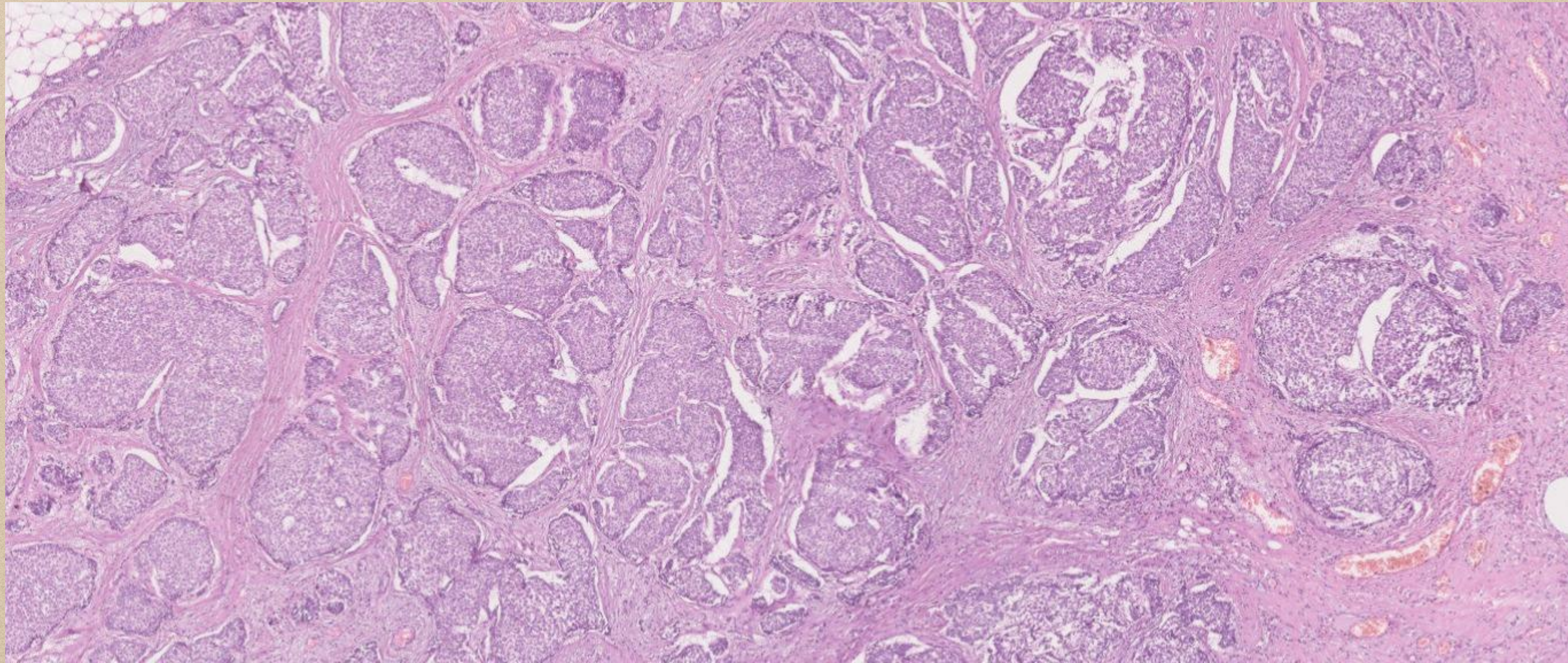
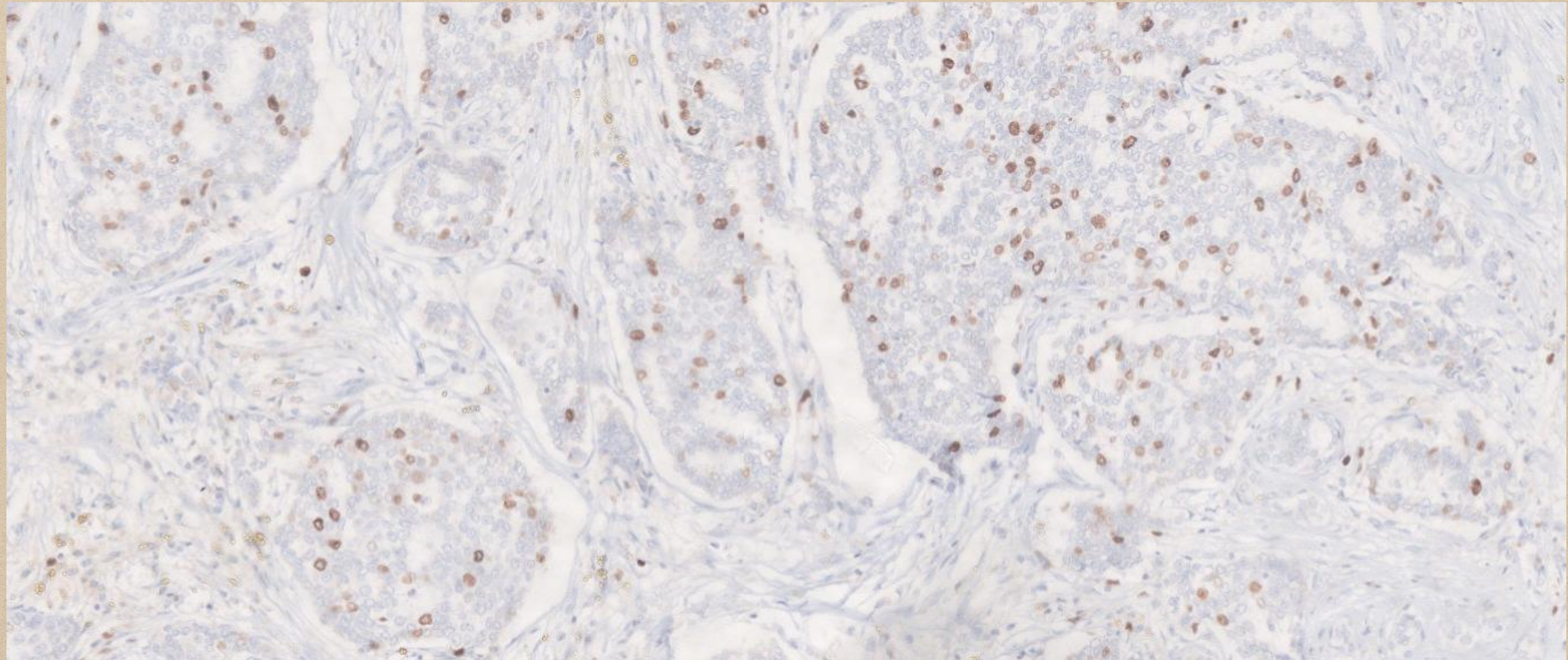H&E:2x: Tumor cells arranged in nests and jig-saw pattern
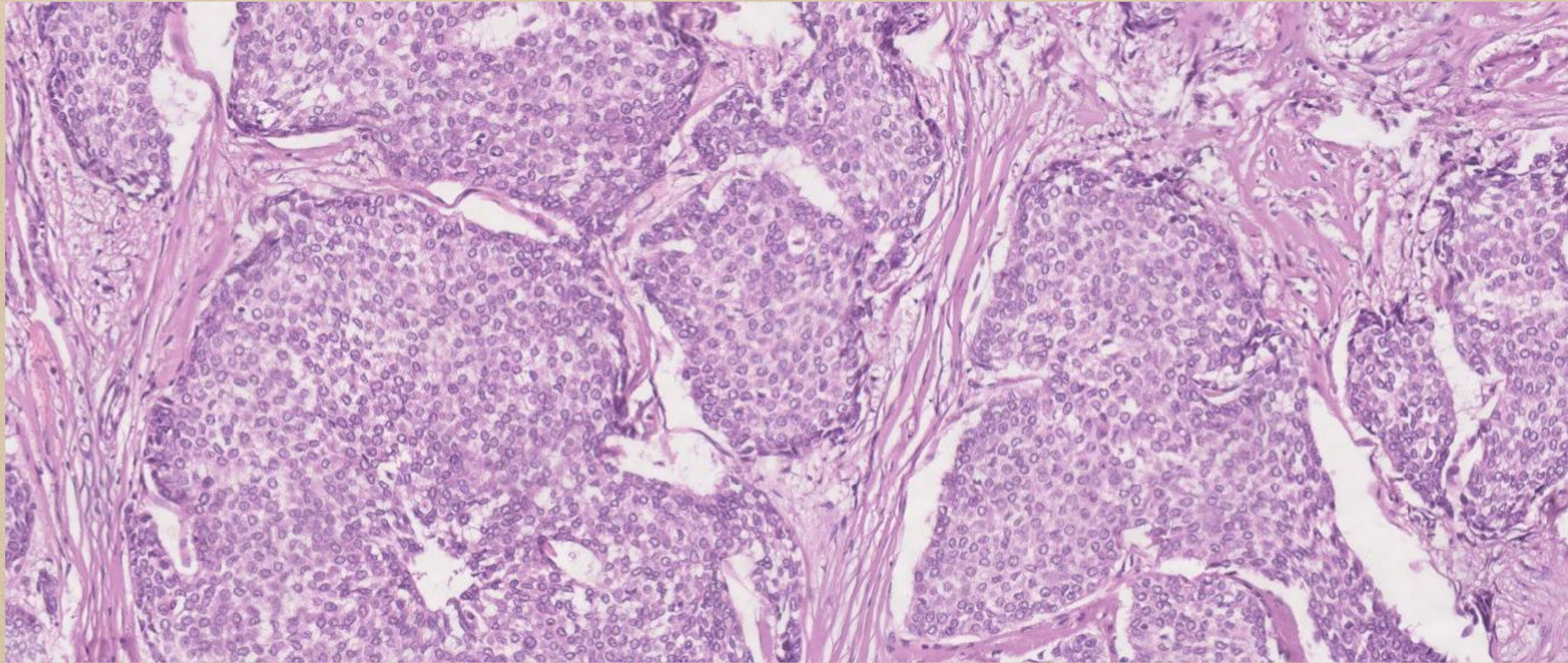
H&E: 10x: Monomorphic Tumor cells with eosinophilic cytoplasm
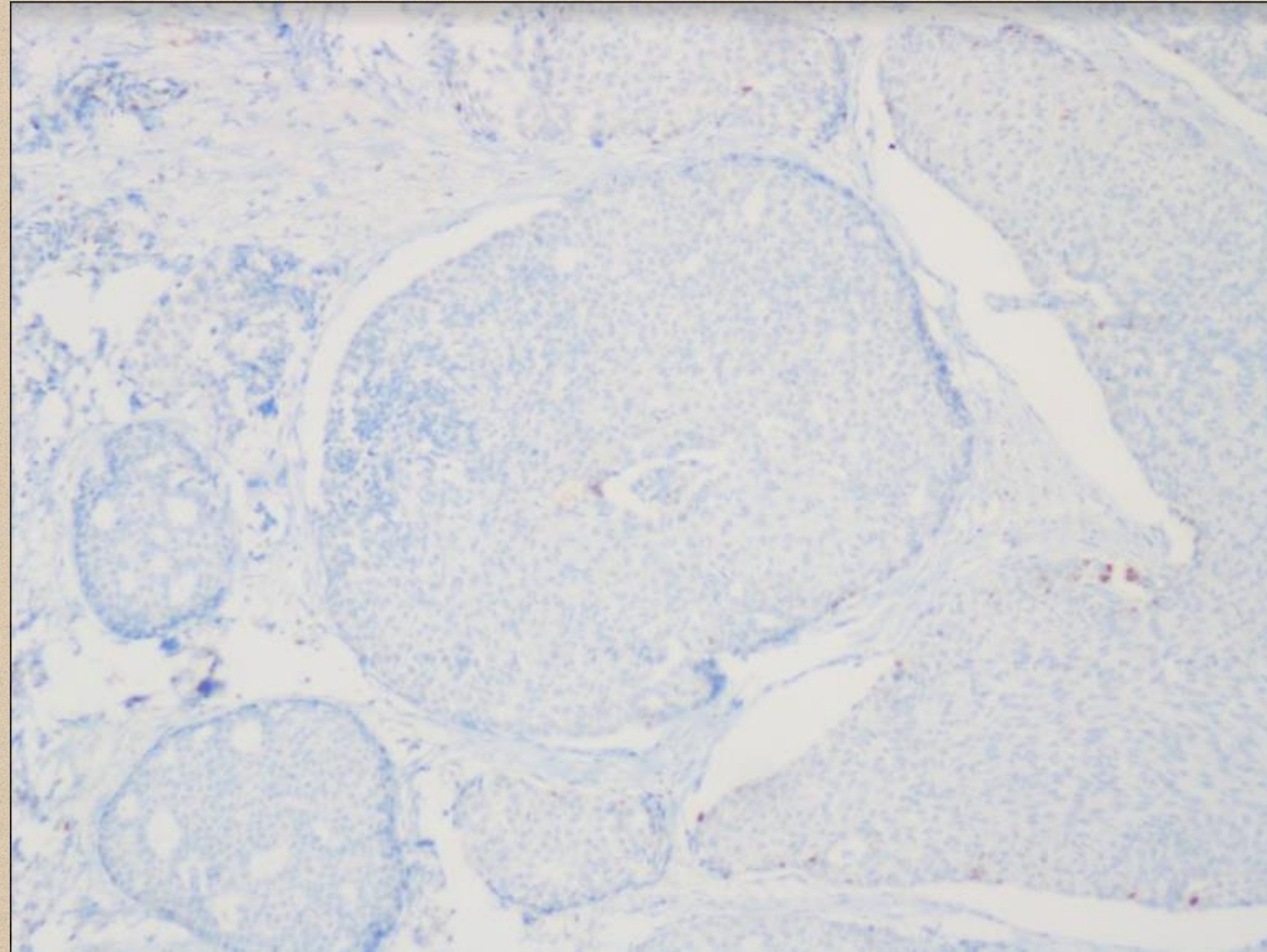
H&E:40x: Tumor cells with ovoid nuclei and prominent nucleoli

Diffuse positive Synaptophysin expression by Tumor cells

Ki-67 proliferation index

Negative immunoexpression of p63 around
the lining myoepithelial cells

Final Impression

- Based on the Histomorphology and IHC findings, a diagnosis of Neuro - Endocrine Tumor, Gr II, Left Breast was made

- pStage: pT2N0

- The tumor cells also showed ER Positivity

- Presence of DCIS component --> Supported a diagnosis of Primary Breast NET

- Grading done as per Criteria for Invasive Breast Carcinoma

Case II

- 61/F, presented with Left Breast lump x 1 month duration, associated with mild pain. No discharge or nipple retraction

- FNAC (Outside Report) – Favour Adenocarcinoma

- Primary Lesion Biopsy(Outside Report) – Infiltrating Ductal carcinoma, Grade II

- PET Scan – FDG avid lesion with spiculated margins in left lower quadrant of Left Breast, with few non FDG avid Left Level 1 Axillary Lymph Nodes

- Patient underwent left modified radical mastectomy with axillary lymph node dissection

- On gross examination, single tumor measuring 1.5 x 1.2 x 1.2 cm was noted in the lower, inner quadrant of the left breast

Histopathology Report - MICROSCOPY

- Sections revealed Infiltrating tumor arranged in nests, organoid , focal trabecular and papillary pattern with round uniform nuclei showing mild anisonucleosis, coarse chromatin and inconspicuous nucleoli

- Focal areas of necrosis seen

- Ductal Carcinoma In Situ(DCIS): Present; with neuroendocrine features, grade II

- On IHC, the tumor cells showed strong positivity for Synaptophysin (100%), Chromogranin and Cytokeratin

- 13 axillary lymph nodes were isolated, 2 showed metastatic tumor deposits (2/13)
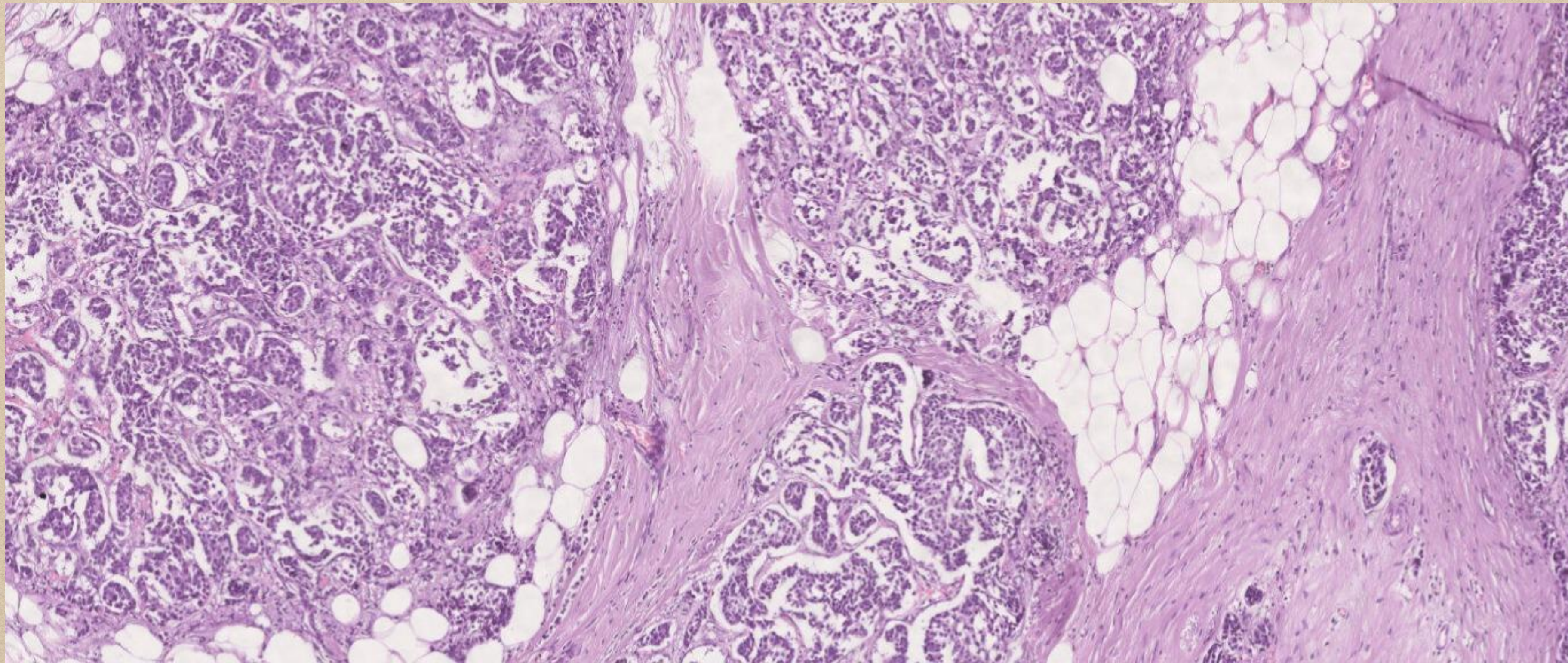
H&E:2x: Tumor cells arranged in nests and organoid pattern
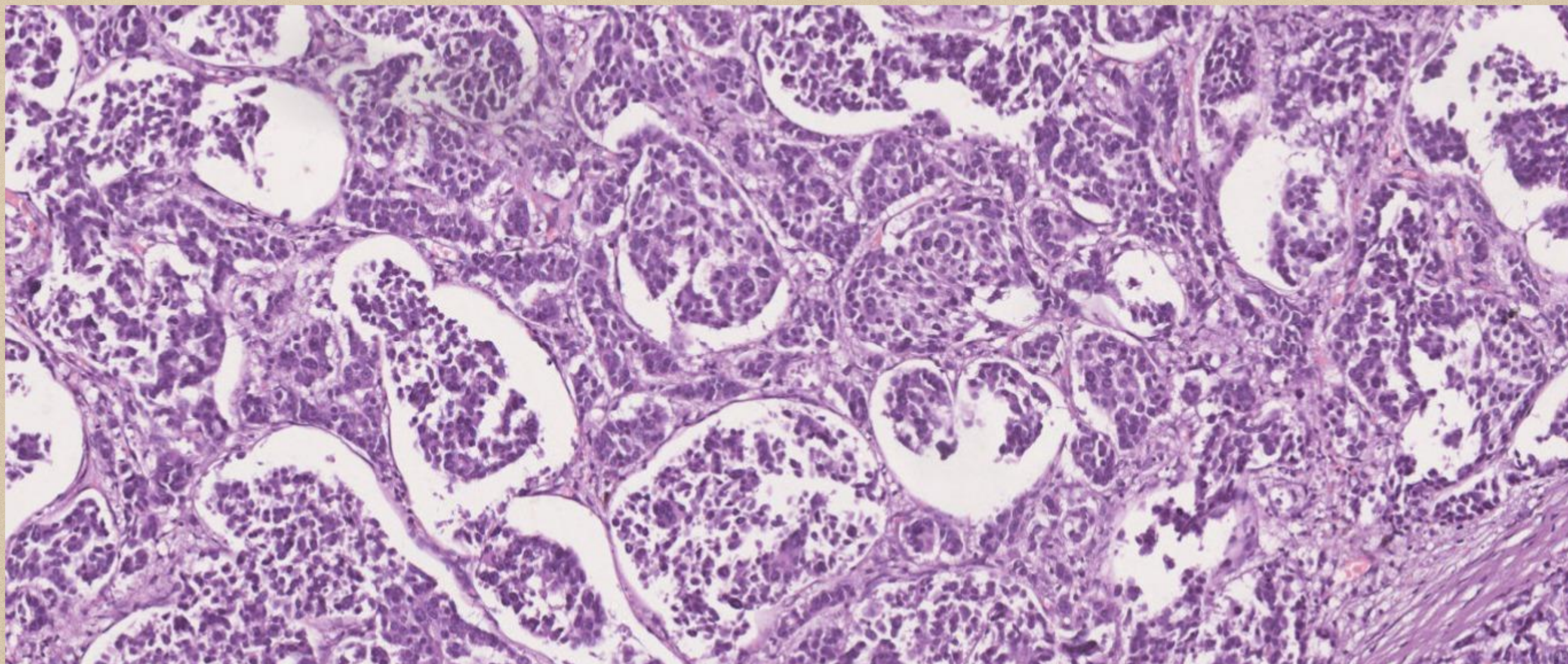
H&E:10x: Tumor cells with round nuclei with mild anisonucleosis
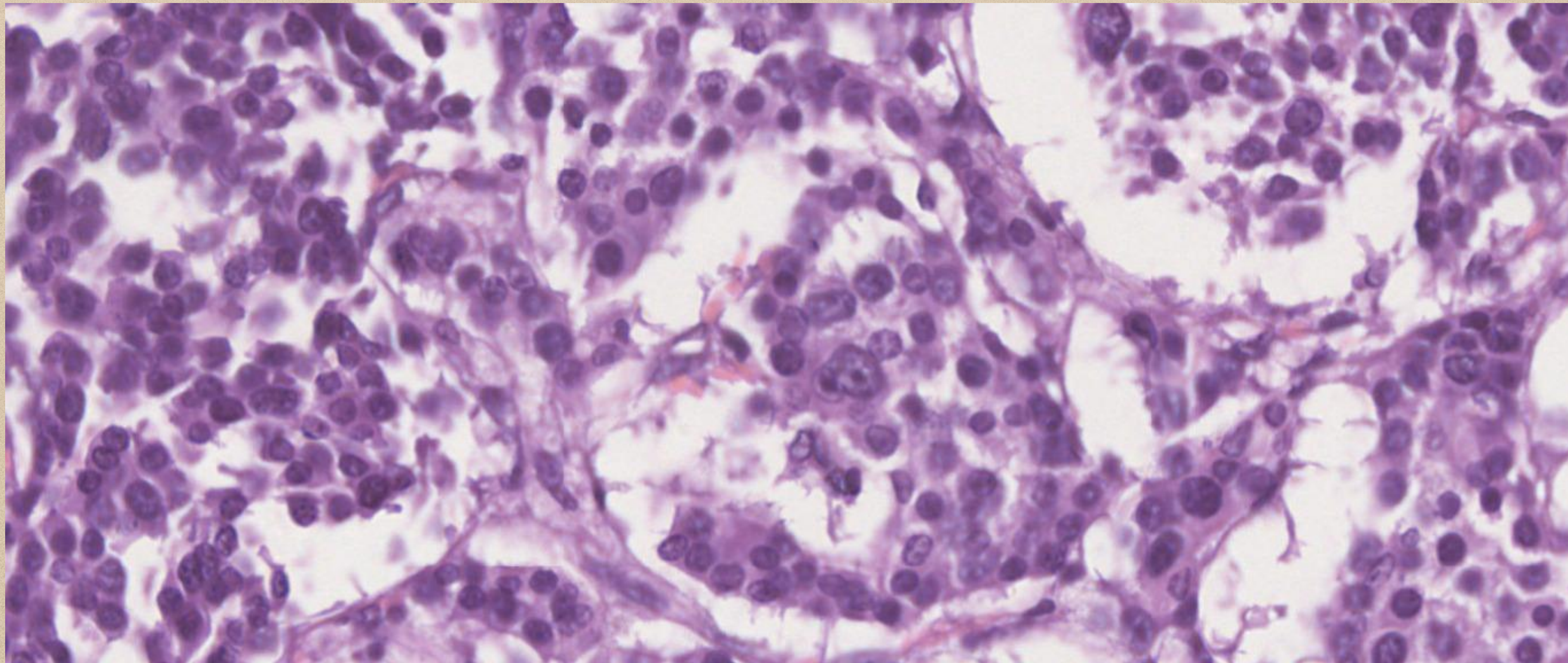
H&E:40x: Tumor cells with anisonucleosis and nuclei with coarse chromatin

Synaptophysin expression by Tumor cells
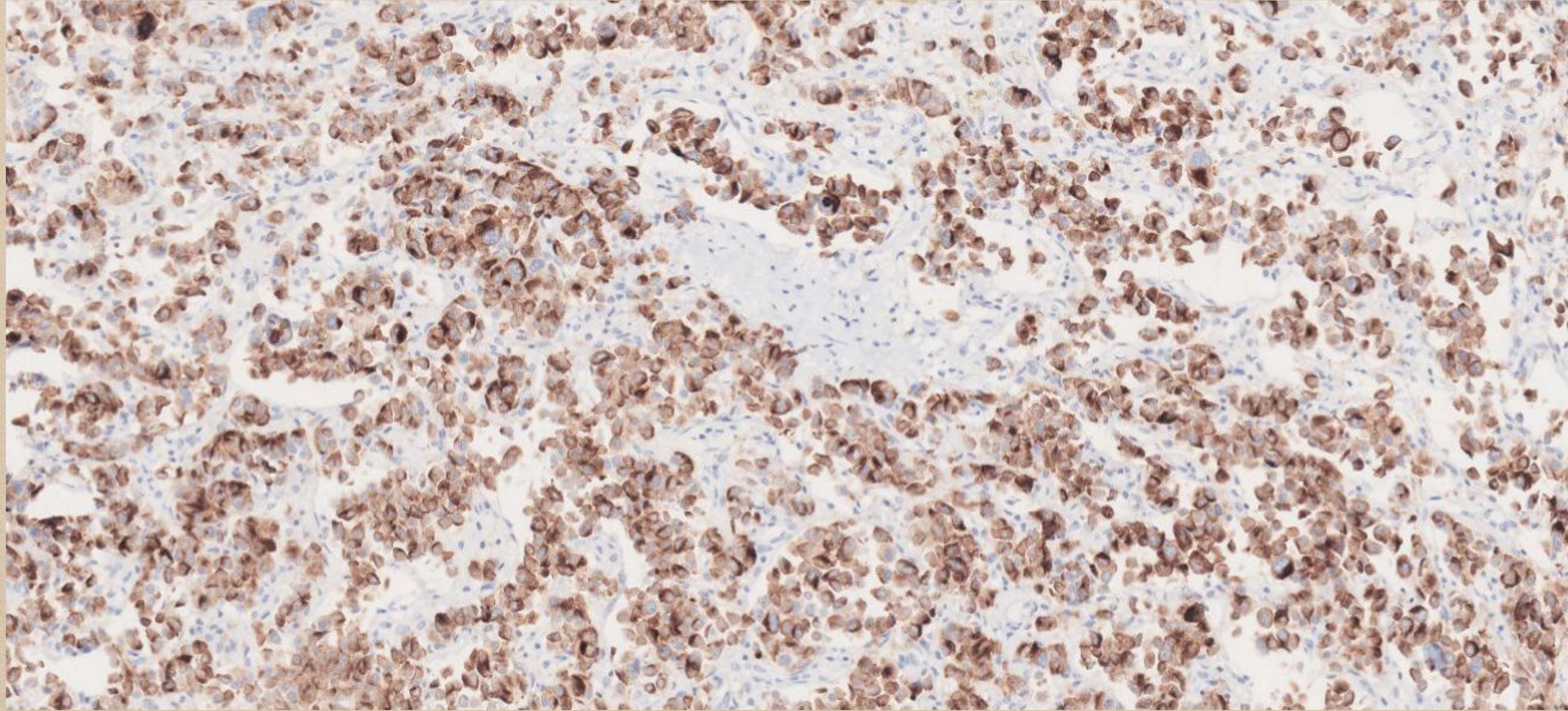
Chromogranin expression by Tumor cells
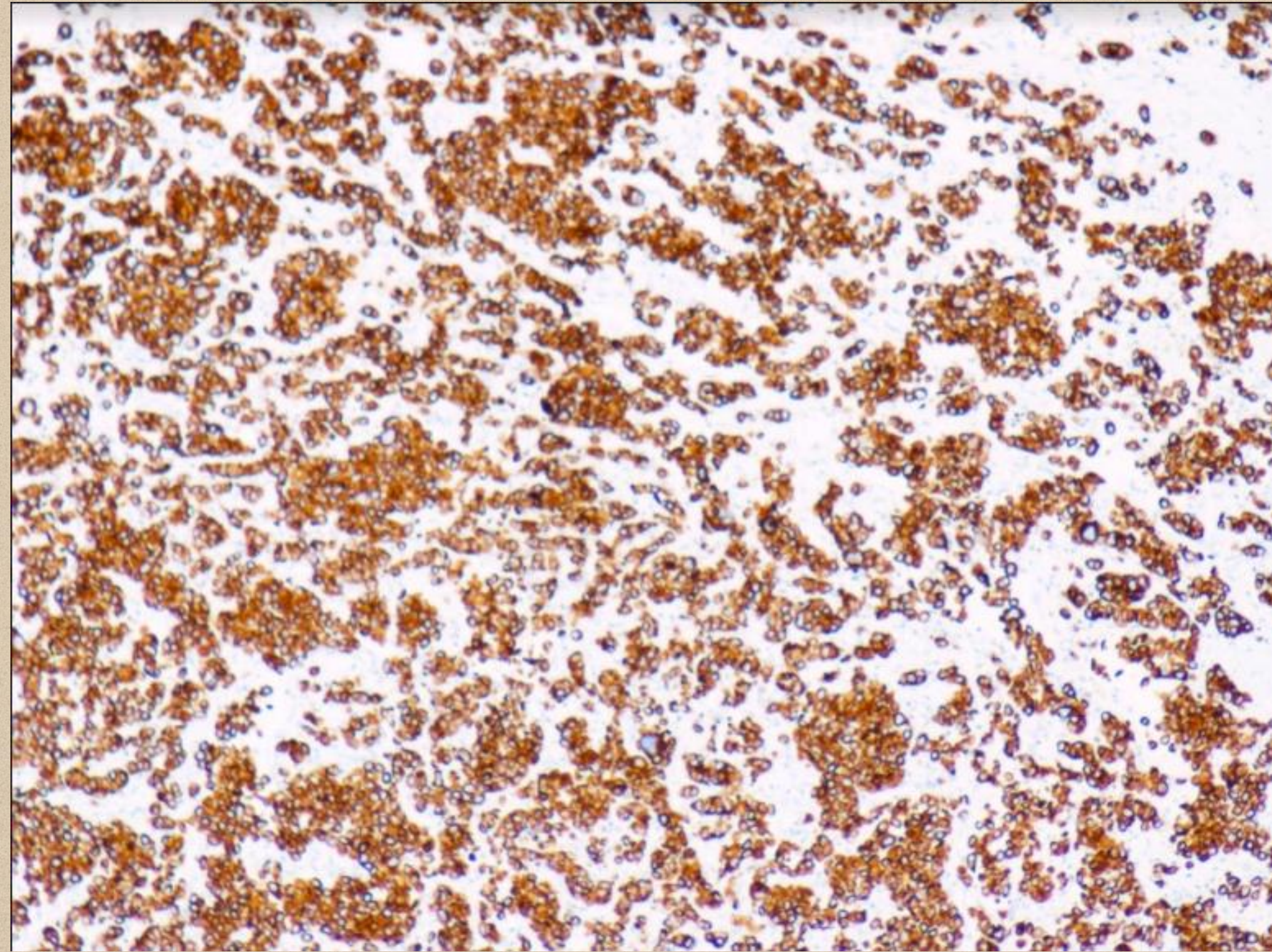
Tumor cells show strong Cytokeratin expression

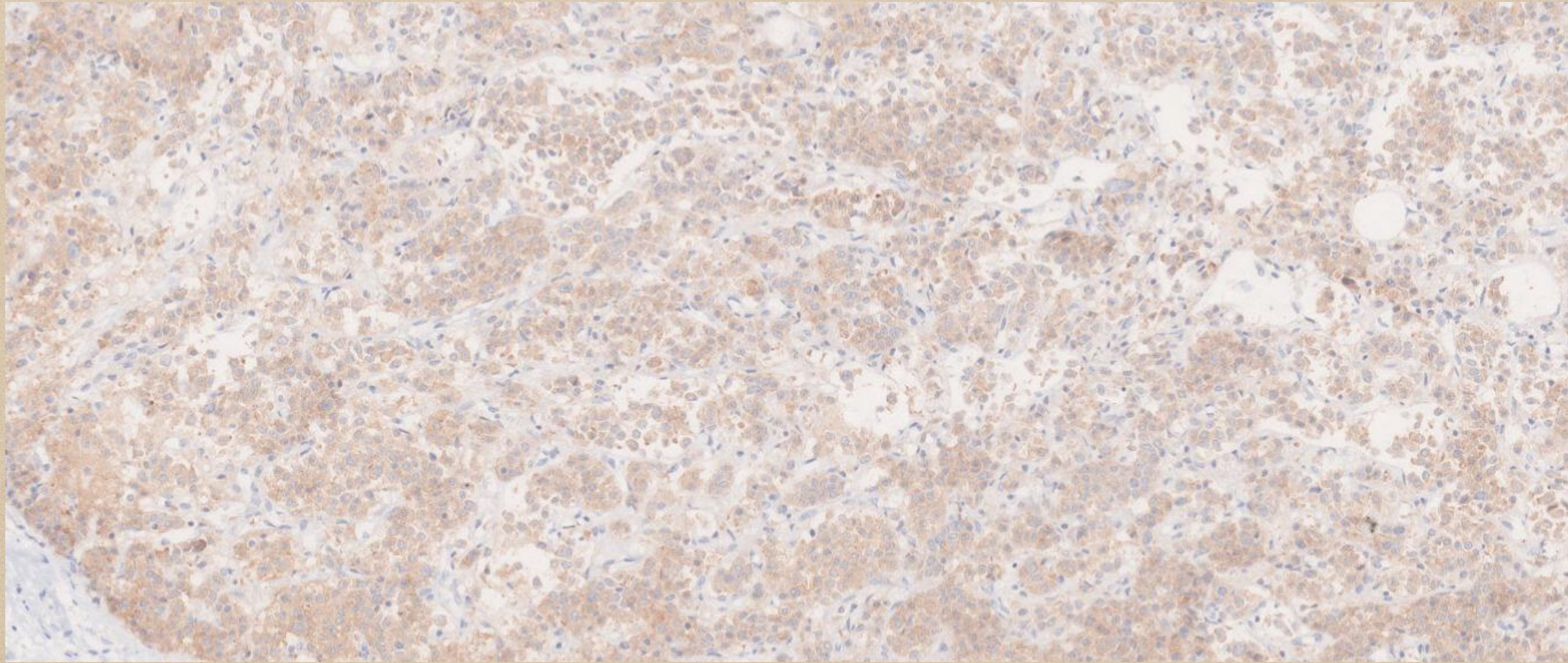# Final Impression

- Based on the Histomorphologic and IHC findings, a diagnosis of Neuro - Endocrine Tumor, Gr II, Left Breast was made

- pStage - $pT_{1c}N_{1a}$

- The tumor cells showed ER Positivity

- Presence of DCIS, Lymph Node Metastasis --> Supported a diagnosis of Primary Breast NET

- Grading done as per Criteria for Invasive Breast Carcinoma

Discussion

- Primary Neuroendocrine Tumors (NET) of the breast are rare

- They represent less than 1% of breast carcinomas and approximately 50% of cases designated as carcinoma with neuroendocrine differentiation as defined in 2012 fourth volume WHO Classification of tumors of the Breast

- Most patients are in 6 th or 7 th decade of life

- Definition: Neuroendocrine tumor (NET) is an invasive tumor characterised by low-intermediate neuroendocrine morphology, supported by the presence of neurosecretory granules and a diffuse, uniform reactivity for neuroendocrine markers.

- These tumors are thought to arise from endocrine differentiation of the breast carcinoma

- The most accepted theory is that neuroendocrine differentiation arises from divergent differentiation of neoplastic cells into epithelial and endocrine cell lines during early carcinogenesis

- Sapino et al in 2001 proposed the first diagnostic criteria for NETs of the breast, suggesting that tumors with greater than 50% expression of neuroendocrine markers be classified as Primary Neuroendocrine breast carcinomas

- Clinically, there are no remarkable differences in presentation from other types of breast carcinomas. NETs may present as an isolated hard breast lump with or without axillary lymphadenopathy
- On mammogram, they are heterogenous dense oval or lobulated masses with indistinct margins

- Histologically, NETs of the breast consist of densely cellular, solid nests and trabeculae of cells that vary from spindle to plasmacytoid to polygonal cells with eosinophilic and granular cytoplasm to large clear cells separated by delicate fibrovascular stroma

According to Nottingham grading system, majority of NETs should be Grade I or Grade II

- The most important differential diagnosis to be excluded is a metastatic neuroendocrine tumor from an extramammary site

- Presence of DCIS component on histology supports a diagnosis of Primary breast NET

- Immunohistochemically, these tumors are positive for Cytokeratin, Chromogranin, Synaptophysin, NSE

- As both primary and metastatic tumors show neuroendocrine differentiation, neuroendocrine markers are not useful

- The most specific markers for breast primary are GATA3, Mammaglobin and GCDFP15

- These tumors are more likely to be ER/PR positive and lack Her2 expression

- They frequently express AR and GCDFP15

- The Ki-67 proliferation index is low

- Good prognostic features include early stage, absence of lymph node metastases and ER/PR positive status

- The presence of DCIS component, ER expression, axillary lymph node metastases and the absence of a history of an extramammary primary neuroendocrine neoplasm (NEN) supports the diagnosis of primary breast NET

Essential and Desirable diagnostic criteria:

Essential : histological features and immunoprofile characteristic of neuroendocrine differentiation

Desirable: coexisting ductal carcinoma in situ

Staging:

- NETs are graded according to criteria for other types of Invasive breast carcinomas

Treatment and Prognosis:

- Tumor stage and histological grade are used as main prognostic parameters

- There are no specific guidelines for grading, staging or treatment of primary NETs of the breast

- It is recommended that NETs of the breast be staged and treated similar to conventional cancer

- In conclusion, Primary Neuroendocrine Tumor of the Breast is a rare tumor, classified as a type of invasive mammary carcinoma with distinctive histopathological features

- For diagnosis, metastatic neuroendocrine carcinoma must be ruled out clinically and an in-situ component has to be demonstrated histologically

- The distinction of primary from metastatic NET is critical to avoid misdiagnosis and unnecessary surgical and medical therapy in the latter

- A definitive diagnosis relies on histological and immunohistochemical features

References:

- Rosen LE, Gattuso P. Neuroendocrine Tumors of the Breast. Arch Pathol Lab Med. 2017; 141:1577-1581

- Hejjane L, Oualla K, Bouchbika Z et al. Primary neuroendocrine tumors of the breast: two case reports and review of the literature. Journal of Medical Case Reports. 2020;14: 1-6

- Marinova L, Malinova D, Vicheva S. Primary Neuroendocrine carcinoma of the breast: Histopathological Criteria, Prognostic Factors and Review of the Literature. Case Reports in Pathology. Volume 2016;1-4

- Neuroendocrine tumors of the Breast. World Health Organisation Classification of Tumors of the Breast. Lyon, France: IARC Press;2019:156-158

Thank You