Ear and Temporal Bone Pathology

What you really need to know

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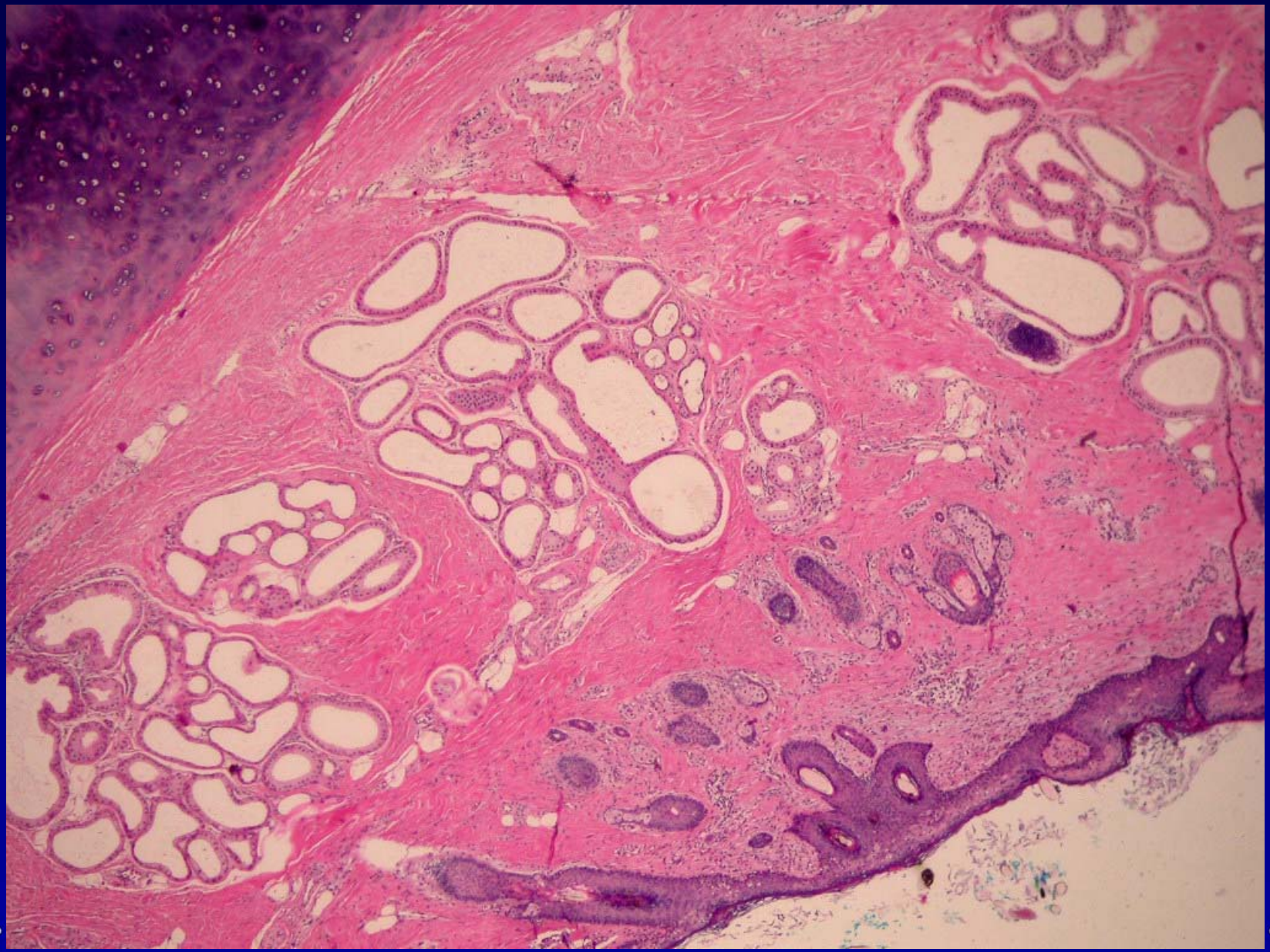
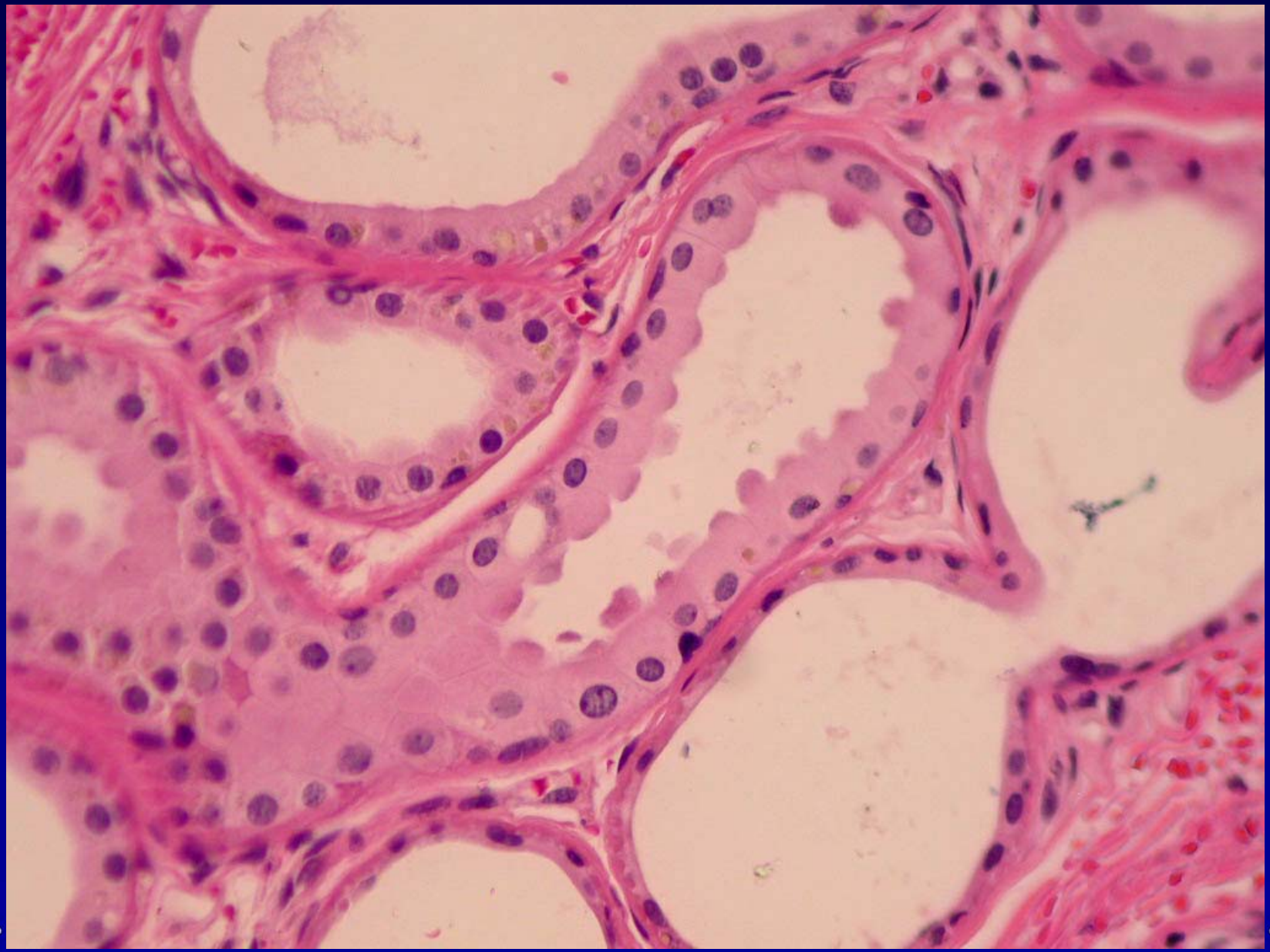
Ceruminous gland tumors

- Ceruminous glands
  - found in the outer 1/3 to ½ (cartilaginous portion) of the external auditory canal
  - estimated number 1,000 - 2,000 in the average ear.
  - Ceruminous glands are not present in the bony part of the EAC.
  - apocrine glands - consist of a coiled tube deep to the sebaceous glands superficial to the perichondrium
  - double layered lining with inner apocrine cells and outer myoepithelial cells.





Ceruminous gland tumors

- Ceruminous gland tumors
  - uncommon and most pathologists and clinicians have little experience with them
  - Dr. Perzin found
    - "76 apparently primary neoplasms occurred in the external auditory canal, including 51 squamous cell carcinomas and 25 tumors of glandular origin, including 10 adenoid cystic carcinomas, nine ceruminous adenomas, and six ceruminous adenocarcinomas".
  - accessioned over a 53 year period in the Laboratory of Surgical Pathology at the Columbia-Presbyterian Hospital, during which they received 395,000 surgical specimens.

Ceruminous gland tumors

- Ceruminoma
  - term has been used to include both malignant and benign ceruminous neoplasms
  - should be avoided by pathologists; more definitive terms should be used whenever possible
- Other terms that have been used to encompass ceruminous gland tumors (benign and malignant) -avoid
  - *Cylindroma*
  - *Hidradenoma*

Ceruminous gland tumors

- Difficulties in diagnosis
  - anatomical problems in securing an adequate biopsy sample
  - confusing terminology of ceruminous gland neoplasms

- Dr. Friedman in his 1993 monograph "Pathology of the ear" concluded:

  "The outlook for all varieties of *ceruminoma* is variable….The behaviour of these neoplasms cannot be predicted from their microscopical features. I have classified them as "intermediate neoplasms" forming a group between benign and malignant neoplasms."

Ceruminous gland tumors

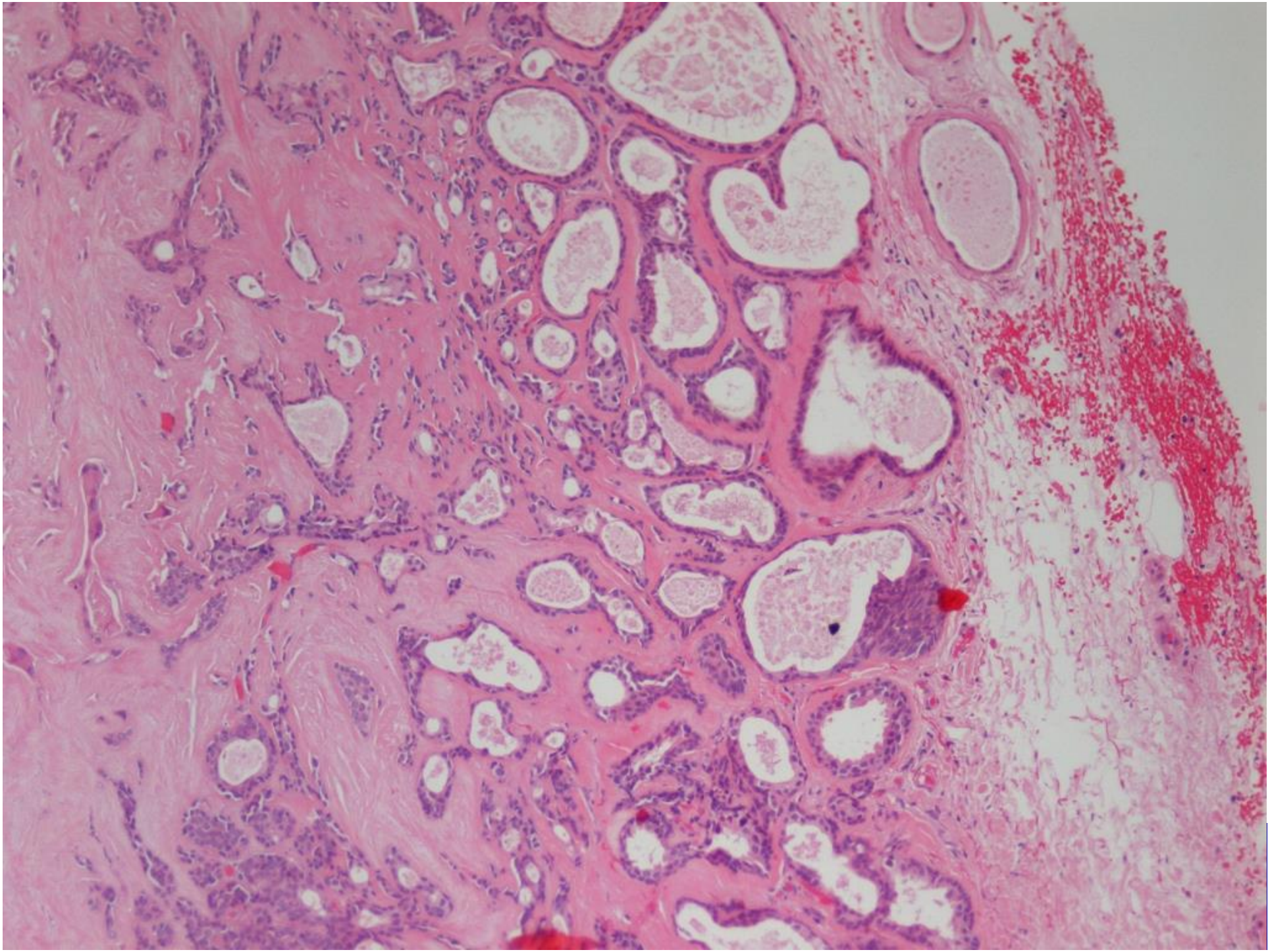
- **Benign tumors**
  - Ceruminous adenoma
  - Pleomorphic adenoma
  - (Syringocystadenoma papilliferum)
- **Malignant tumors**
  - Ceruminous adenocarcinoma
  - Adenoid cystic carcinoma
  - (Mucoepidermoid carcinoma)

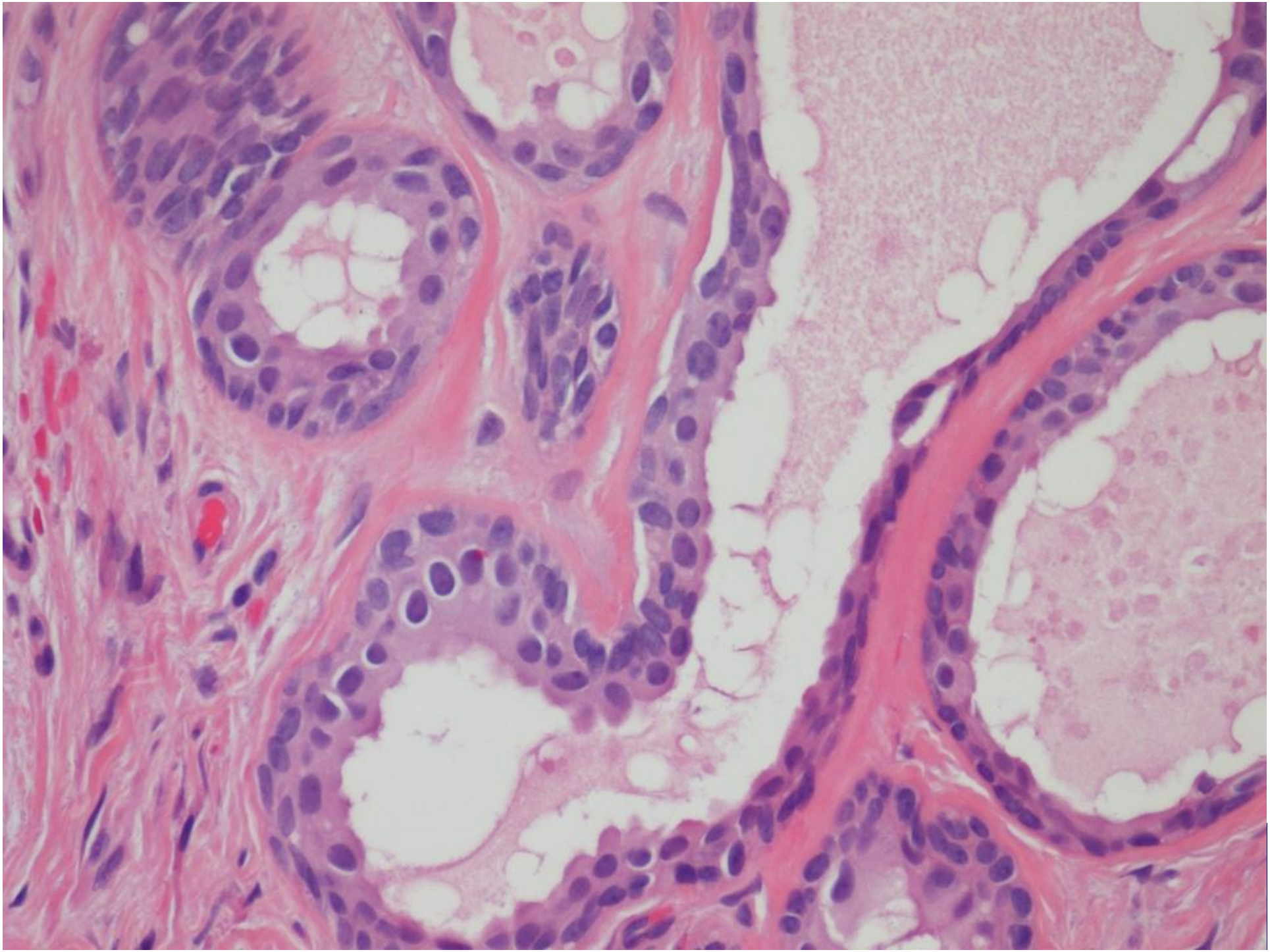
Ceruminous adenoma

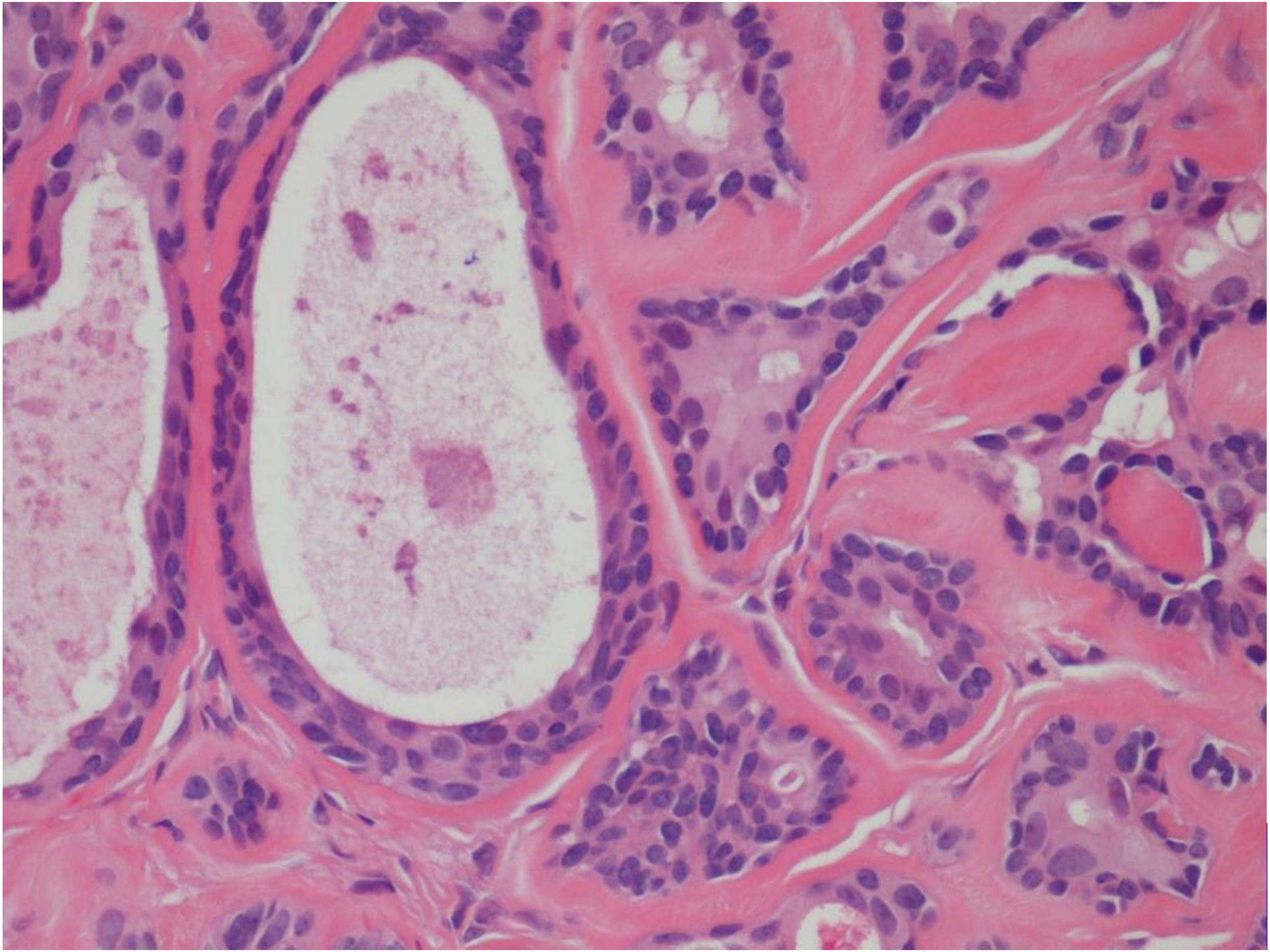
- Ceruminous adenoma (CA) is the most common benign ceruminous gland neoplasm
- recent series of 41 cases of benign ceruminous gland neoplasms reported by Thompson et al from the AFIP - 36 were CA.
- Age range: 12-85 Mean : 52-54 years.
- mild symptoms related to the size of the tumor including hearing loss, facial paralysis, otalgia and rarely bleeding.
- pain and paralysis may be seen in both benign and malignant tumors from this location.
- polypoid or sessile mass in the outer half of the EAC with a mean size of just over 1 cm.

Ceruminous adenoma

- composed of tubal or papillary structures with the most prominent feature being the presence of two distinct cell layers
- inner layer is composed of cells with abundant eosinophilic cytoplasm exhibiting apocrine secretion
- outer myoepithelial layer is spindled to cuboidal
  - CK 5/6, S100, Actin or p63 may be used to highlight this myoepithelial layer.







Ceruminous adenoma - Differential diagnosis

Ceruminal adenocarcinoma

- Many CAC have lost evidence of myoepithelial differentiation - distinction is straightforward.
- Presence of numerous mitoses, nuclear pleomorphism or necrosis would point toward a diagnosis of CAC.

Ceruminous adenoma - Differential diagnosis

Ceruminal adenocarcinoma

- Some CAC are very low-grade tumors that overlap cytologically and architecturally with ceruminous adenoma
- Demonstration of invasion into local structures such as bone, cartilage, blood vessels or nerves

Ceruminous adenoma - Differential diagnosis

- Middle ear adenoma
  - differs in location (middle ear for MEA vs. outer half of EAC for CA)
  - cells in MEA are small cuboidal cells lacking apocrine features
  - myoepithelial differentiation is not present
  - Immunohistochemical identification of neuroendocrine differentiation is also a hallmark of MEA

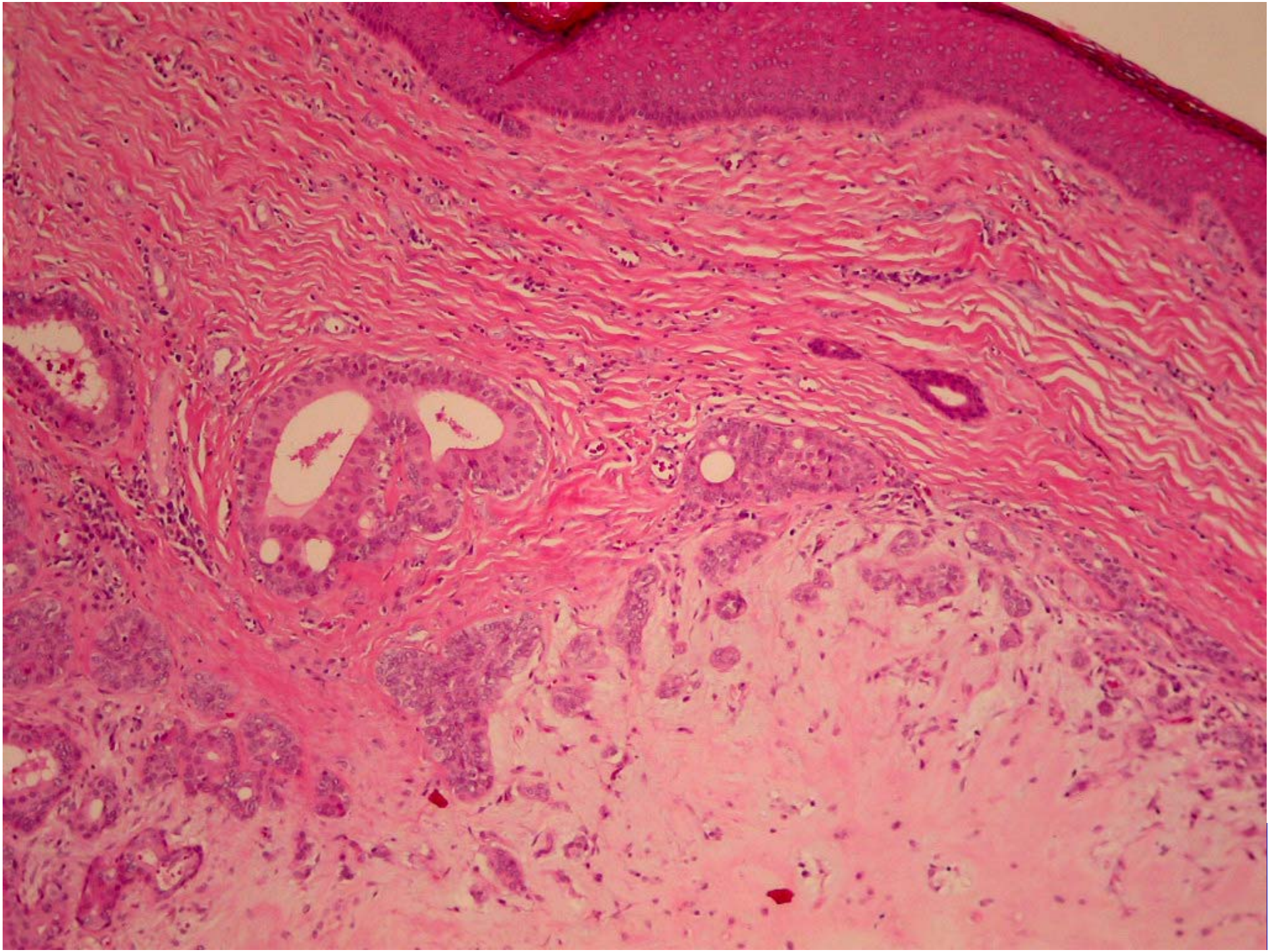
Ceruminous adenoma

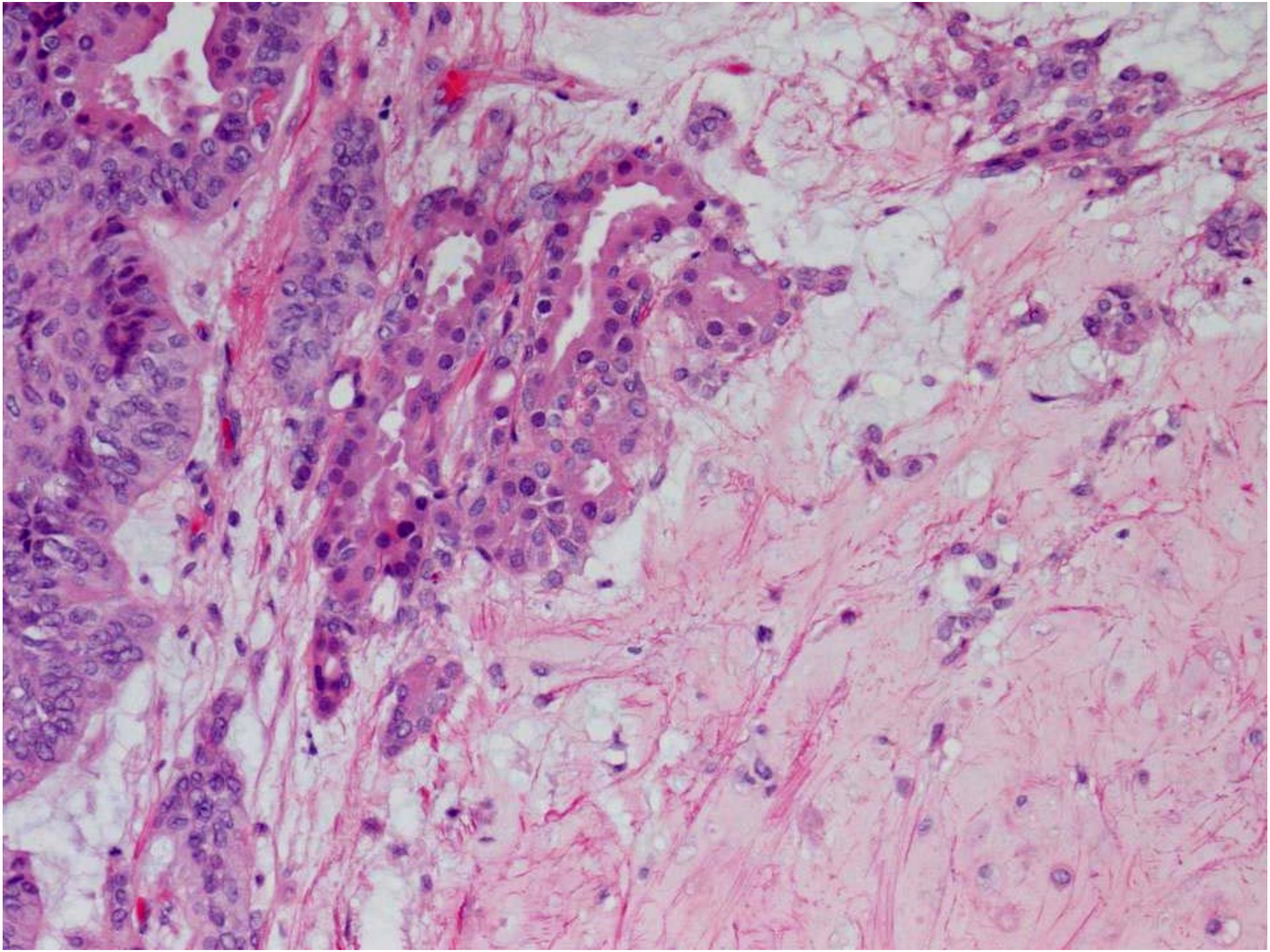
Behavior

- Unresected - continued growth may lead to local tissue destruction
- Recurrences are related to inadequate excision (4 out of 40 in the study of Thompson et al)

Pleomorphic adenoma

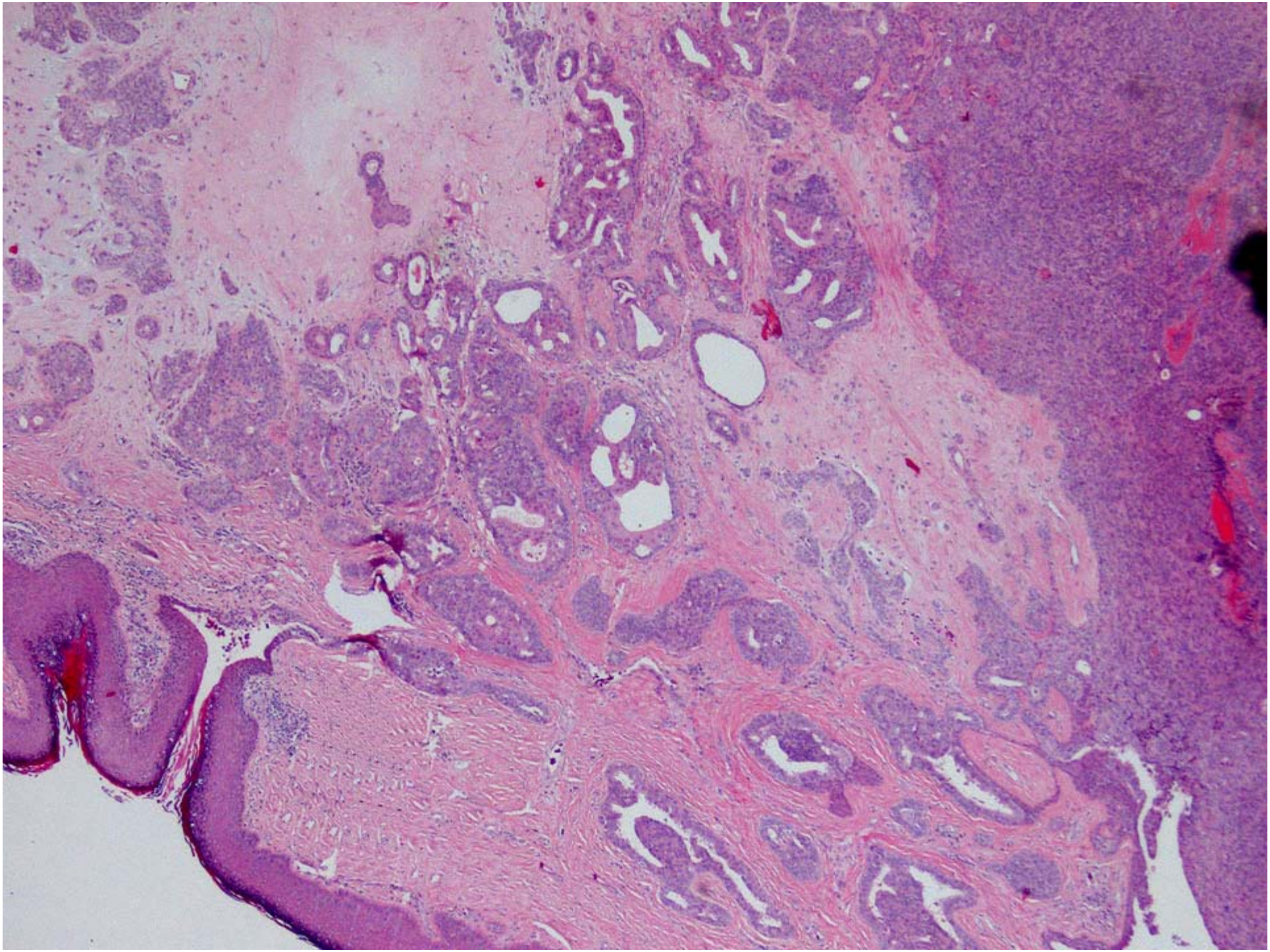
- Pleomorphic adenoma is less common than ceruminous adenoma.
- Of 41 benign ceruminous gland tumors reported by Thompson 4 were PA.
- Their presentation and demographics are similar to CA.

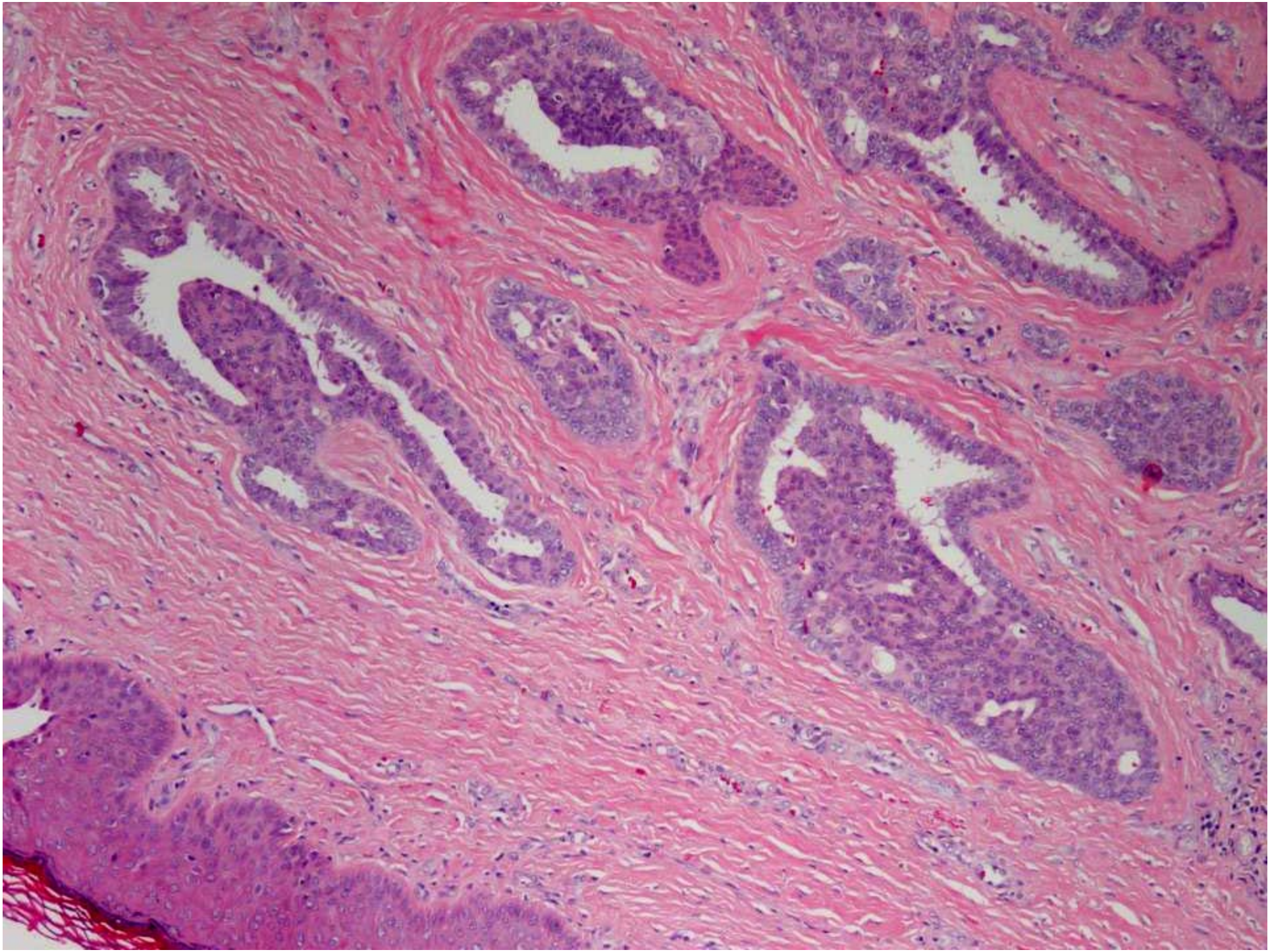


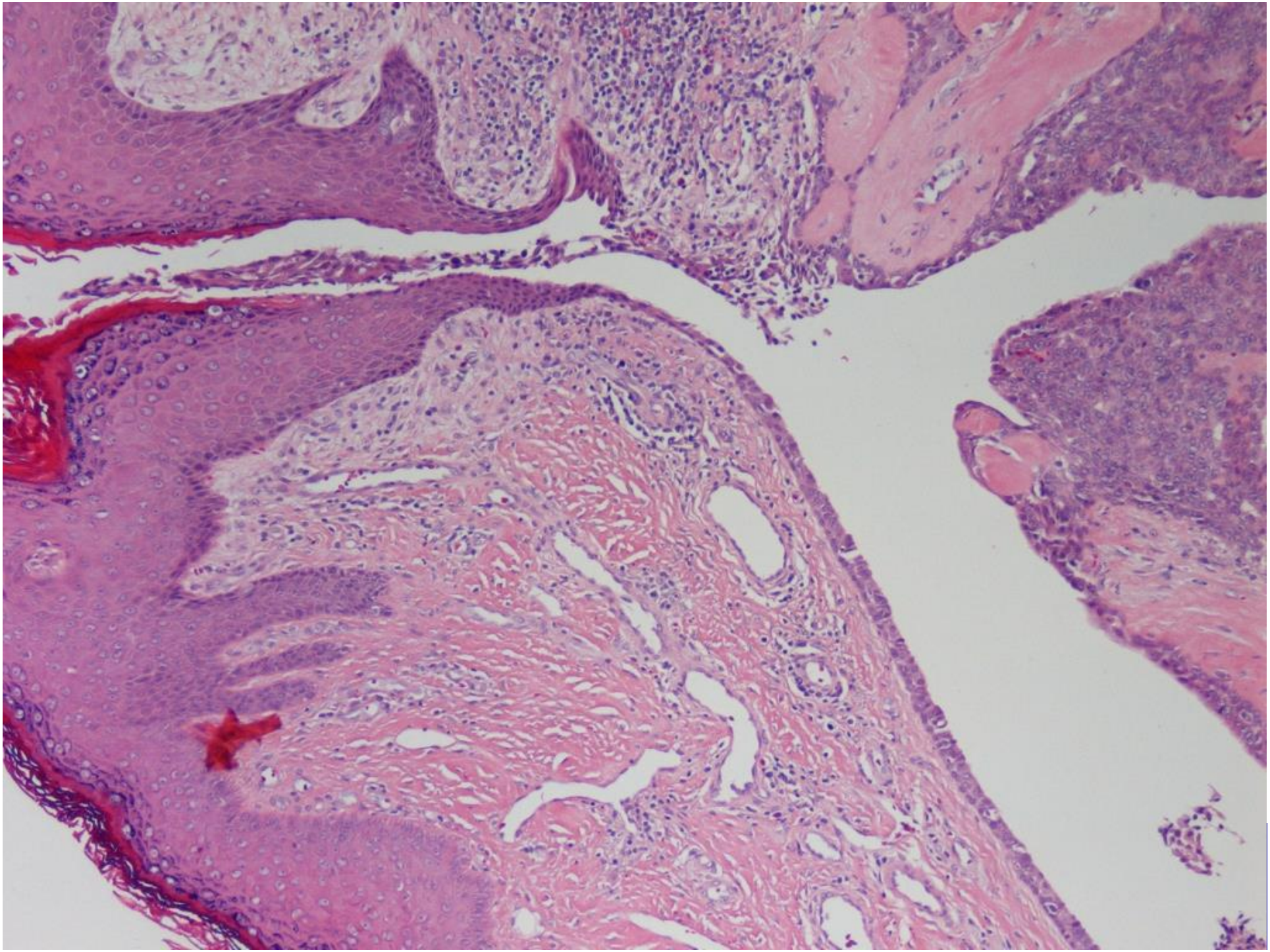


Pleomorphic adenoma – diagnostic issues

- frequently appears less than perfectly circumscribed, particularly in the superficial portion of the lesion
- deep portion will be well circumscribed but not seen until the tumor is resected

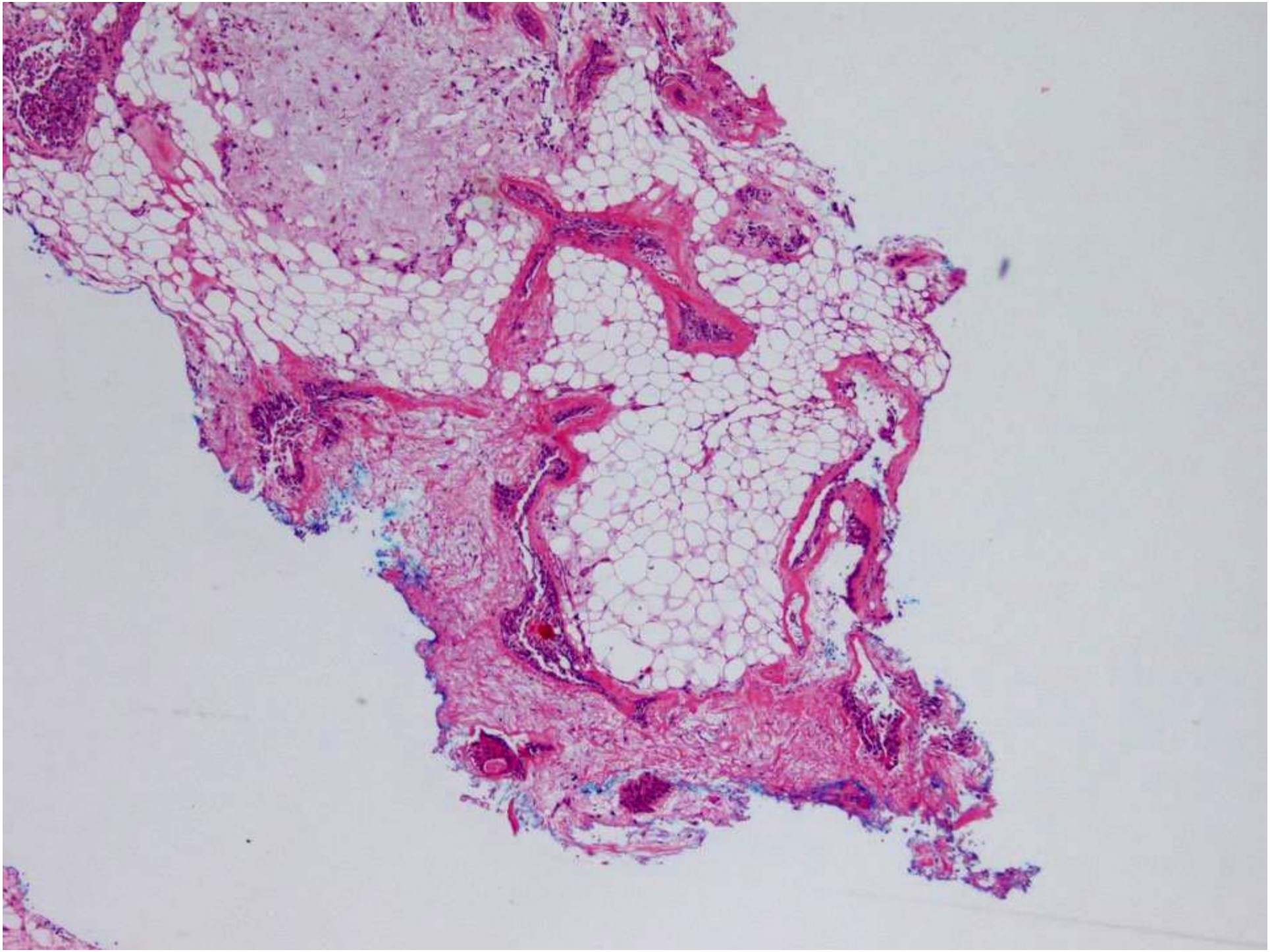


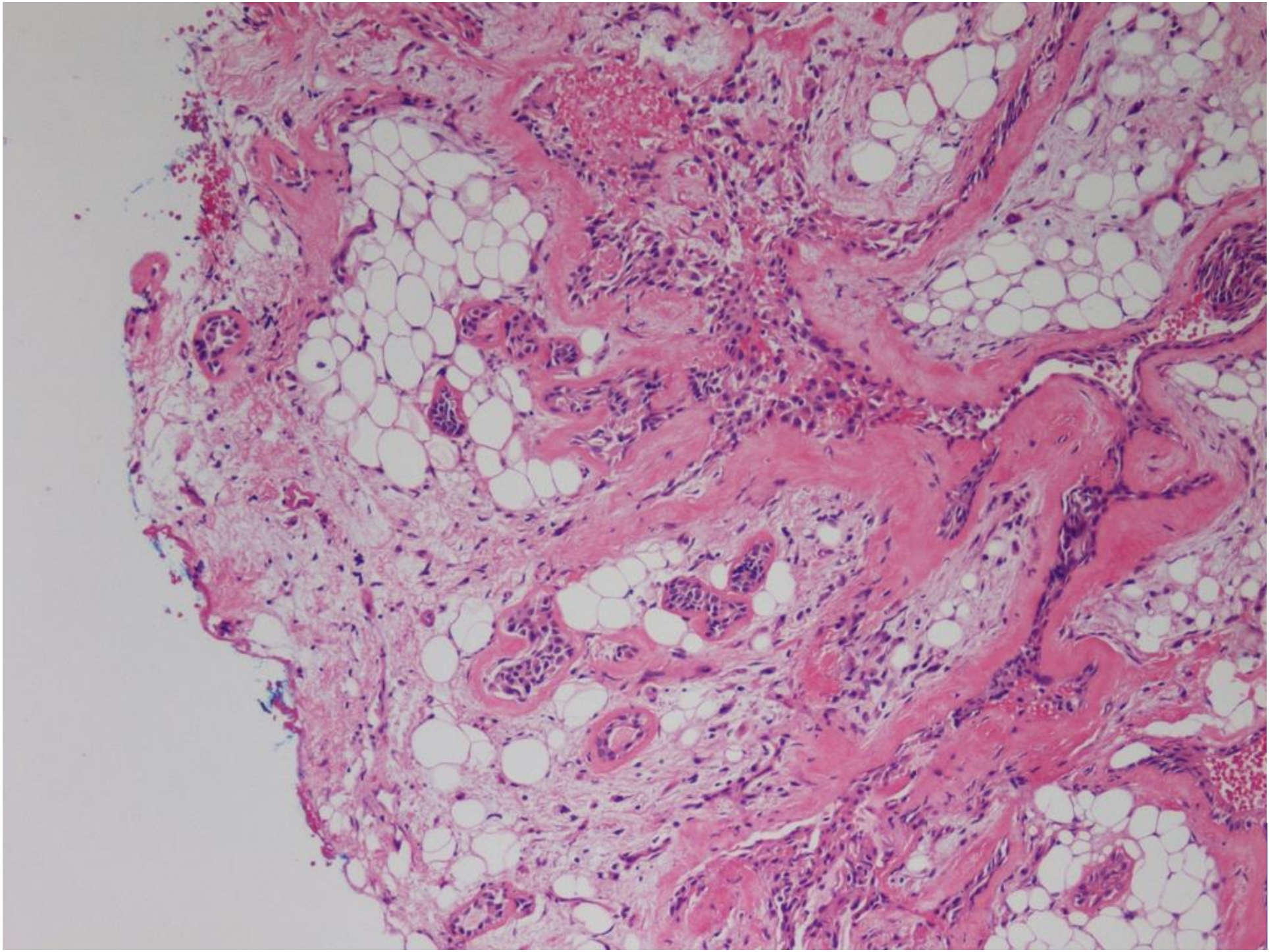


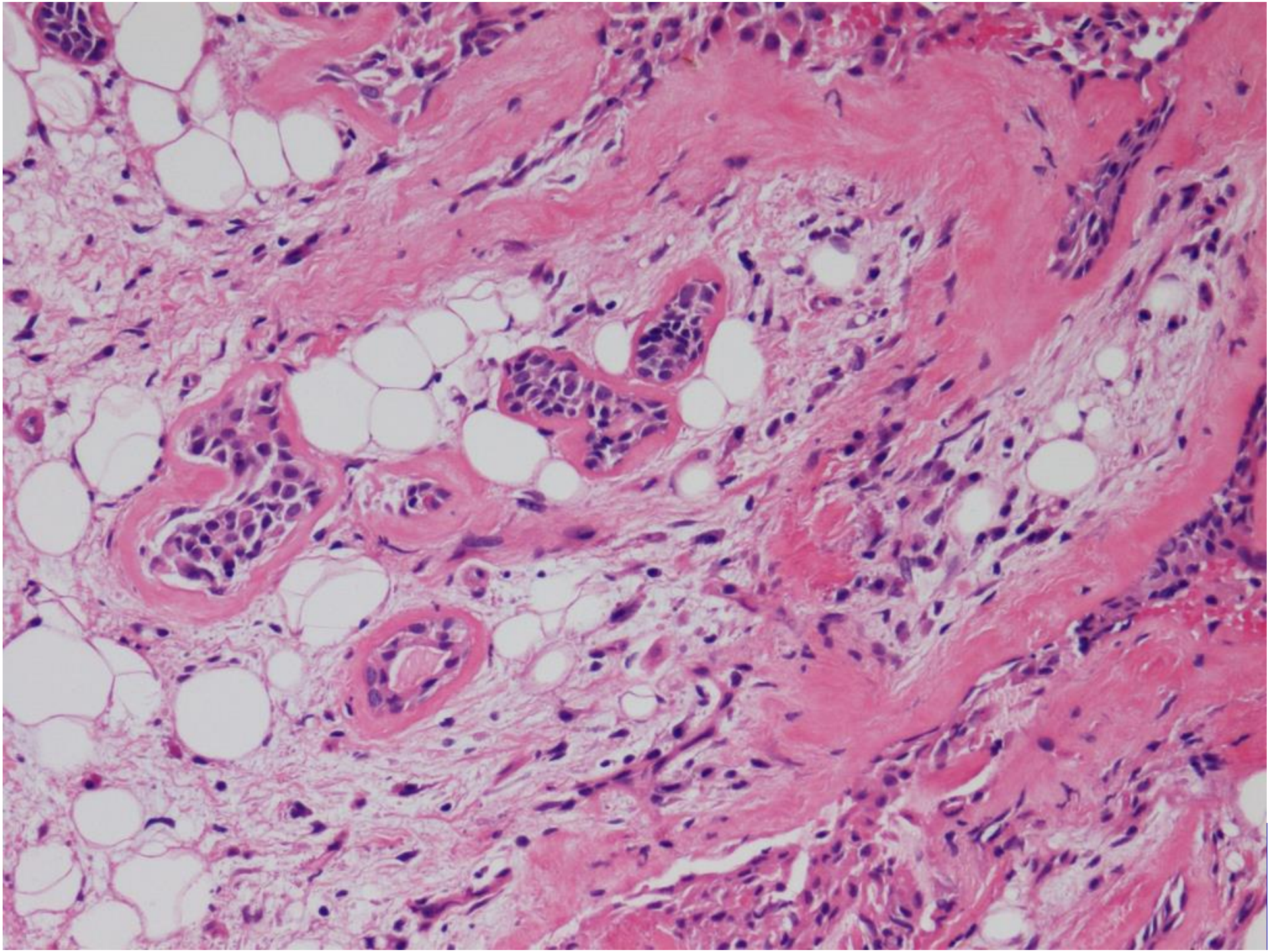


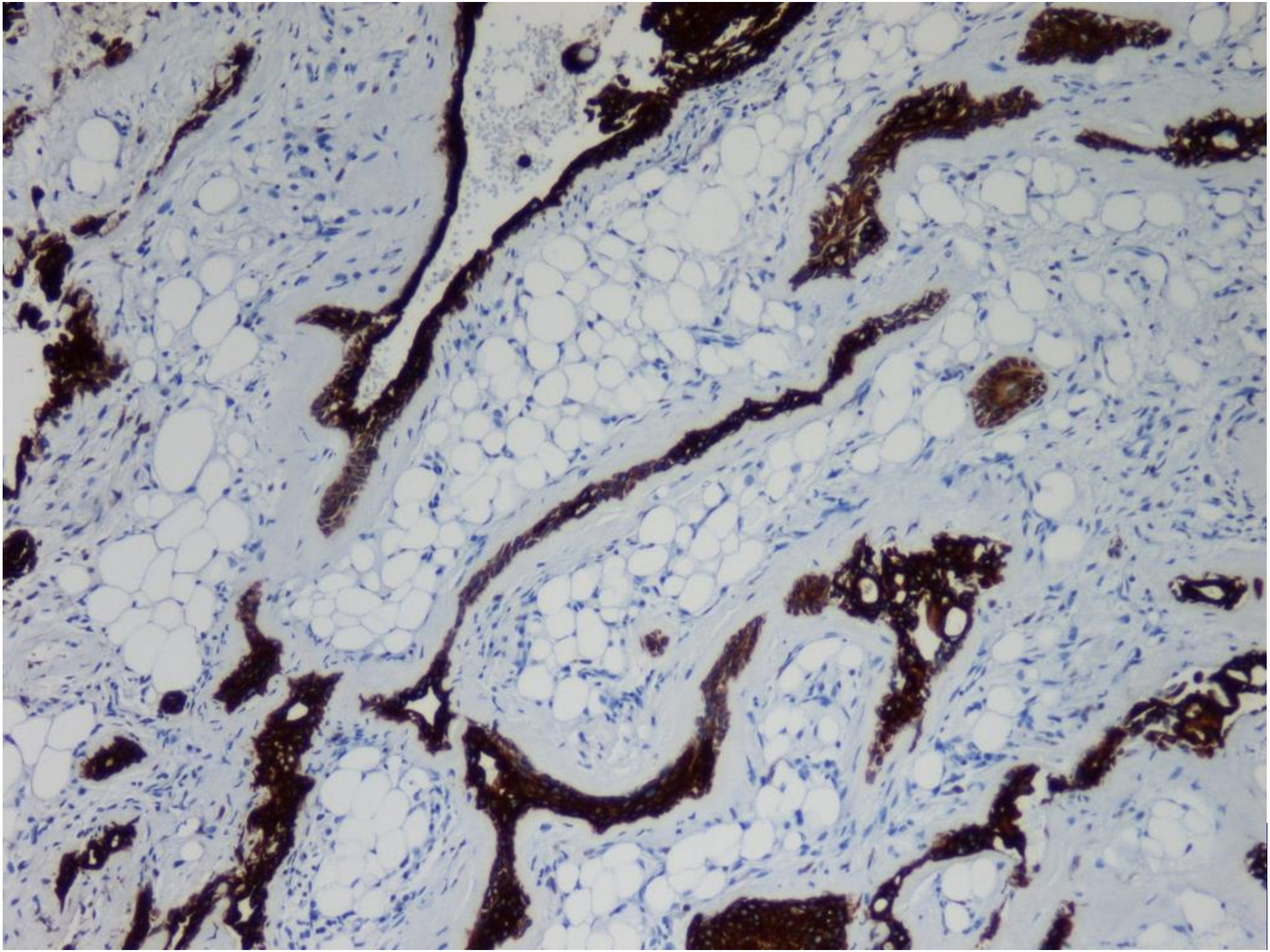
Pleomorphic adenoma – diagnostic issues

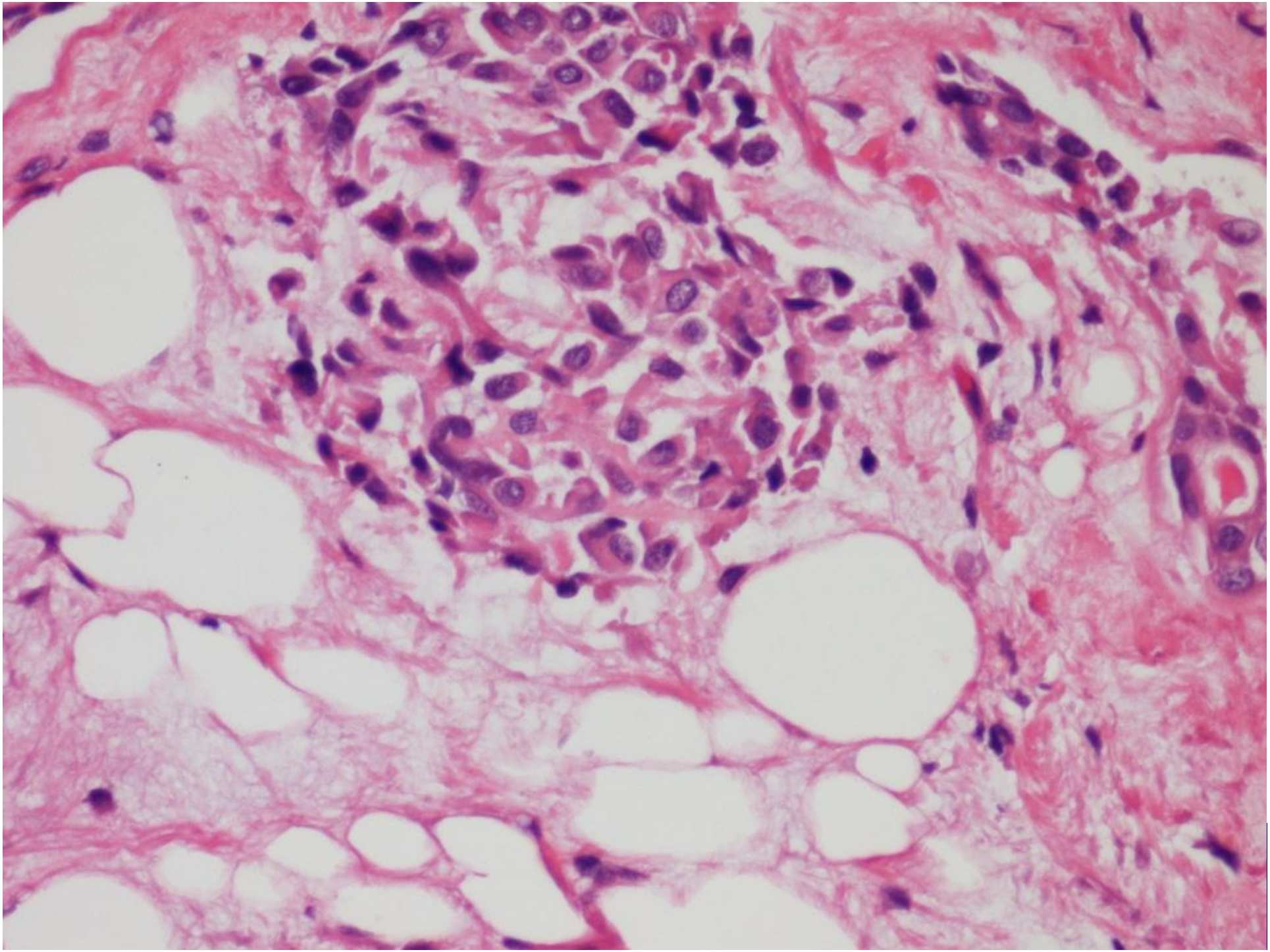
- PA in the external auditory canal may be more inclined to have an adipose cell-rich stroma that leads to a mistaken impression of glands invading through fat. Typically, even in those tumors with extensive adipocytic stroma, myxoid stroma can be identified, at least focally.

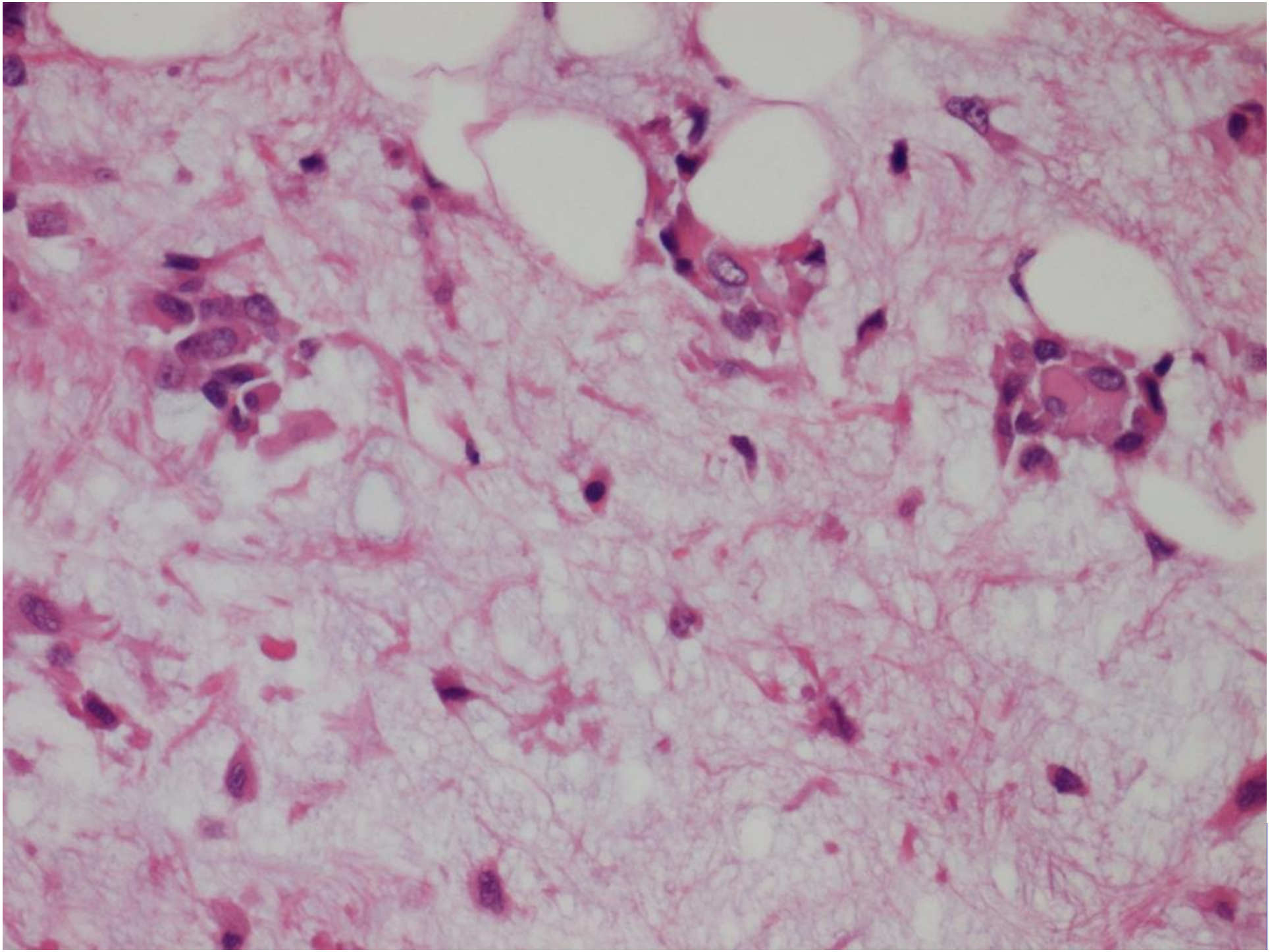


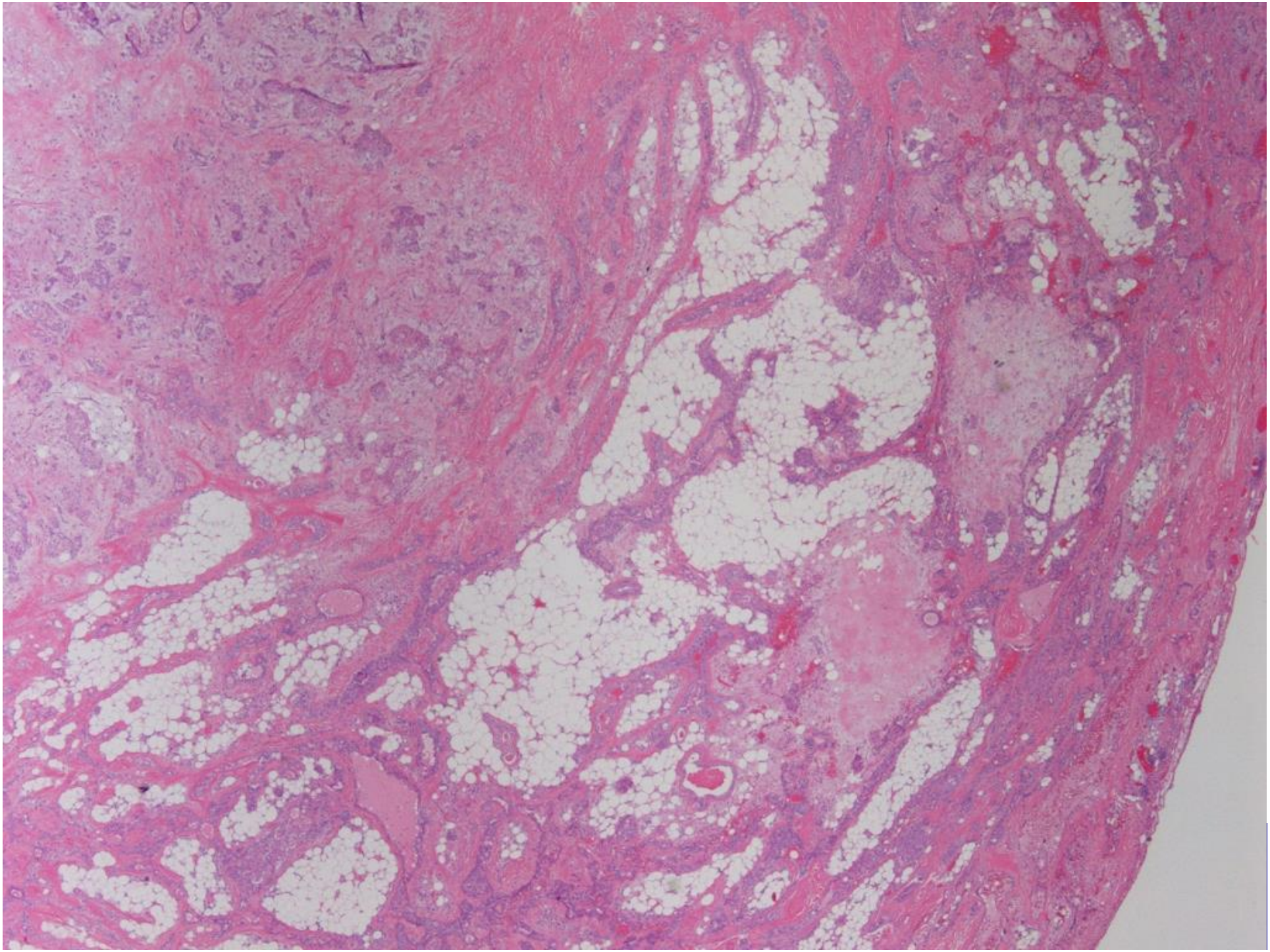


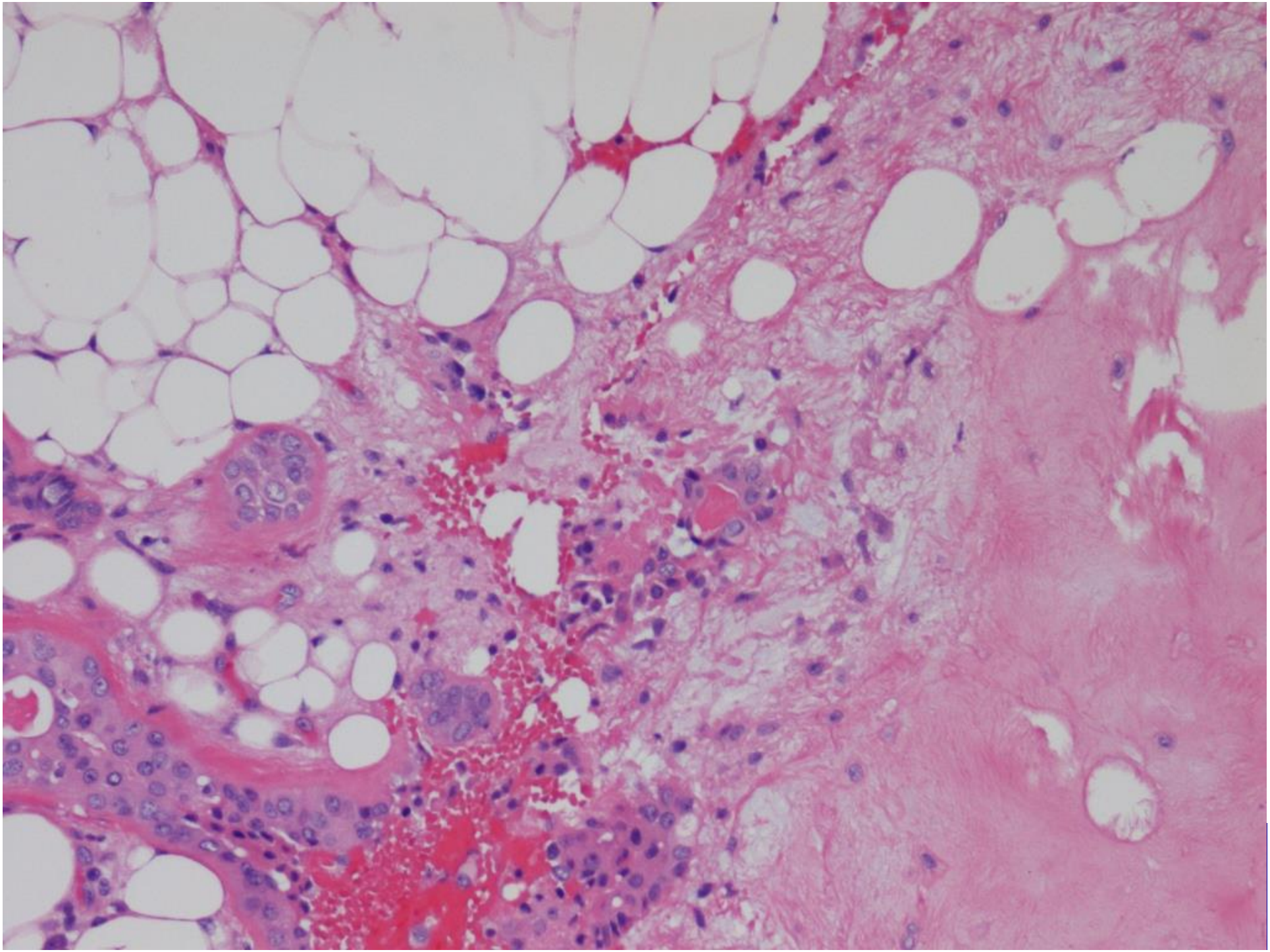












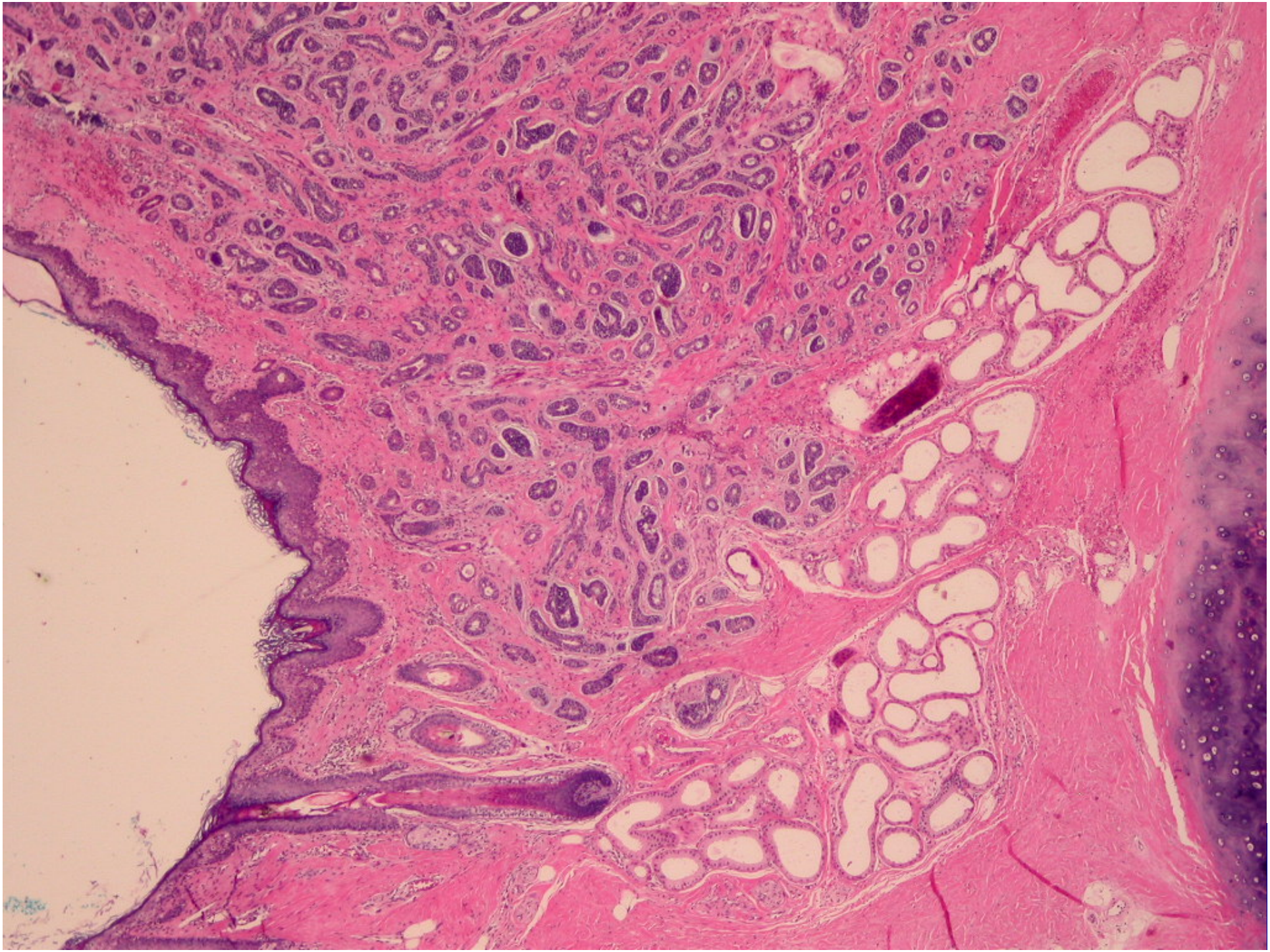
Adenoid cystic carcinoma

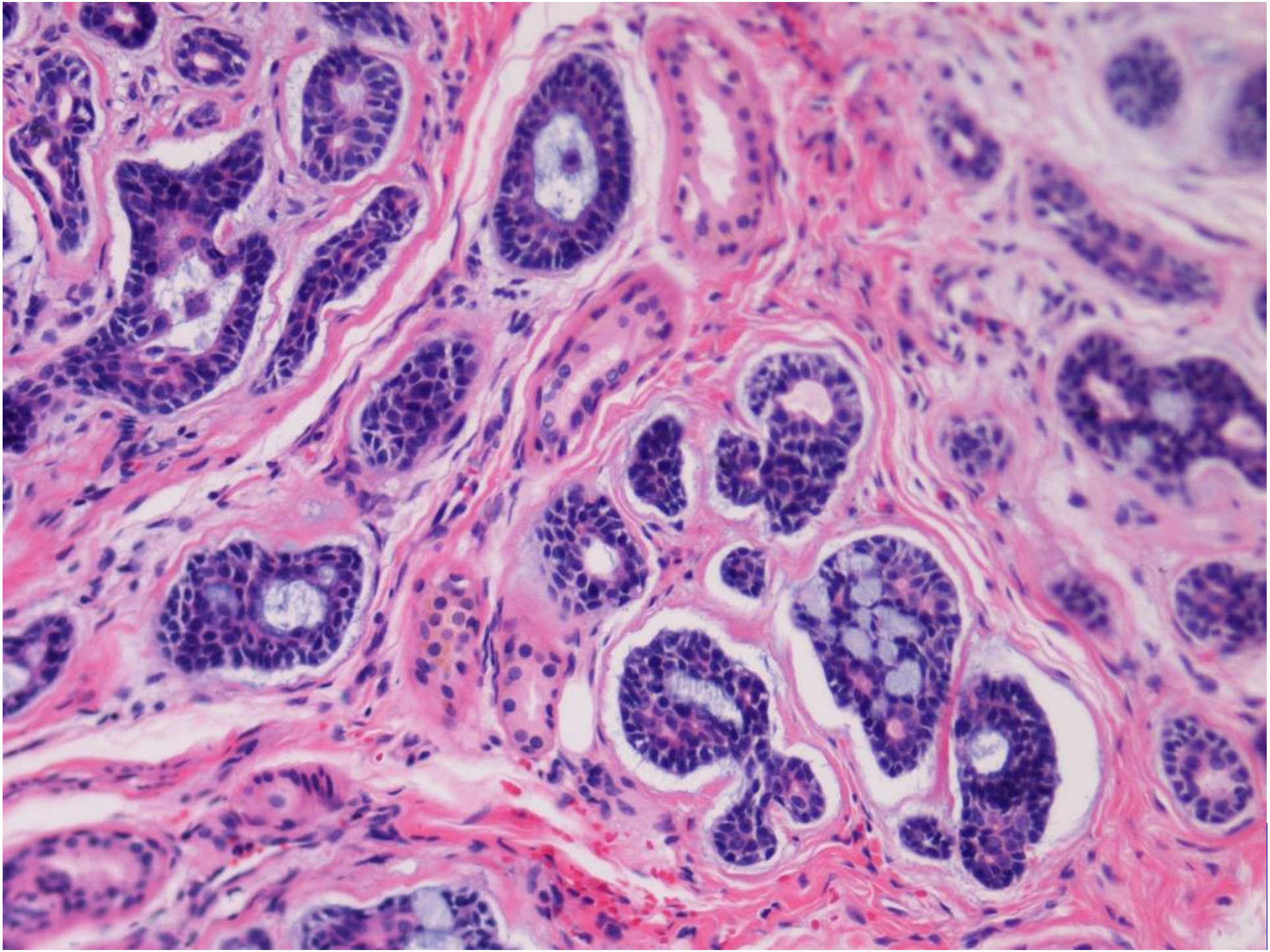
- Adenoid cystic carcinoma is the most common of the ceruminous gland neoplasms in most studies
- Patients are adults with a wide age range, but the average age is in the sixth decade
- Present with a painless or painful nodule or mass, hearing loss or obstructive otitis

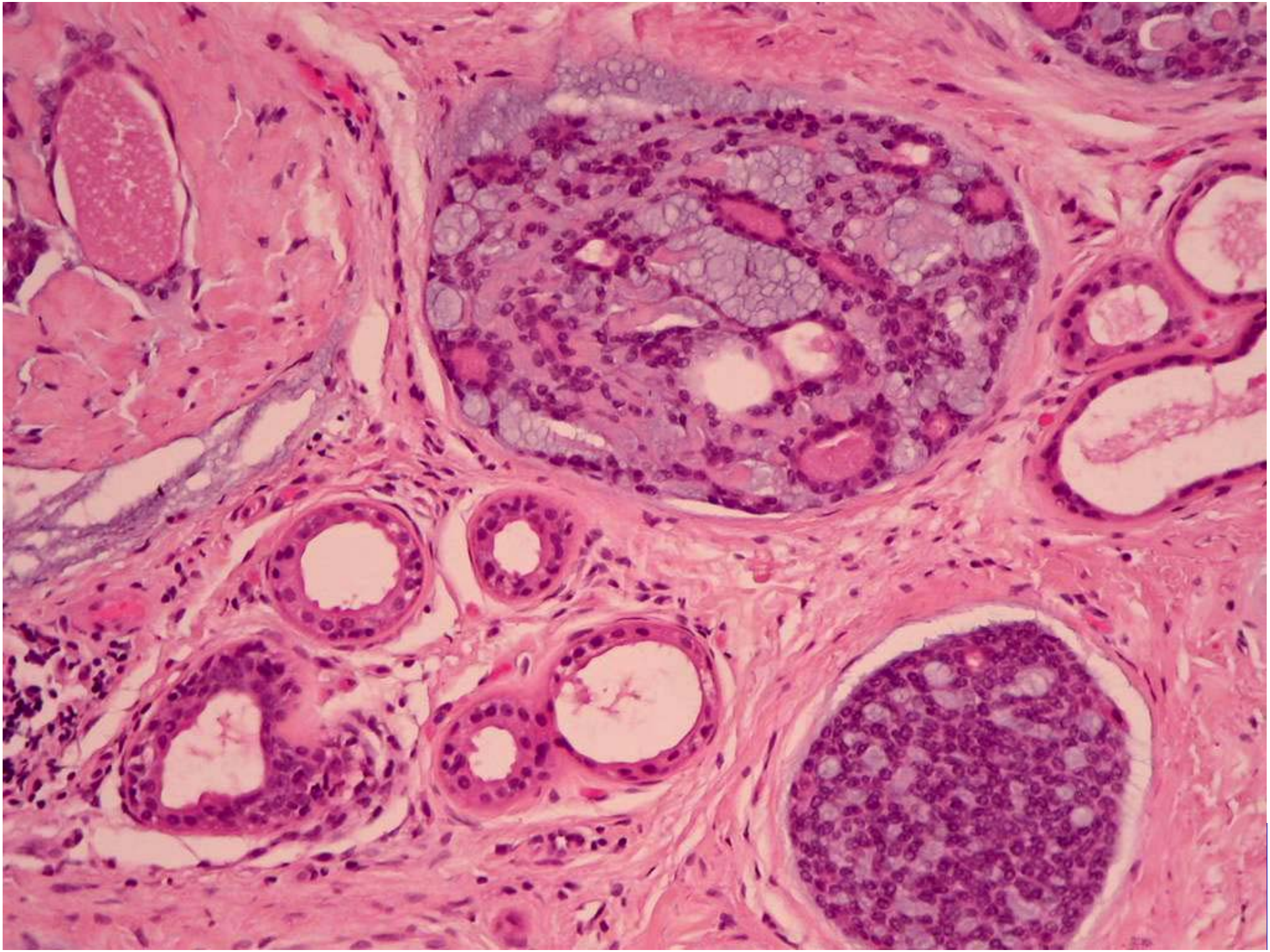
Adenoid cystic carcinoma

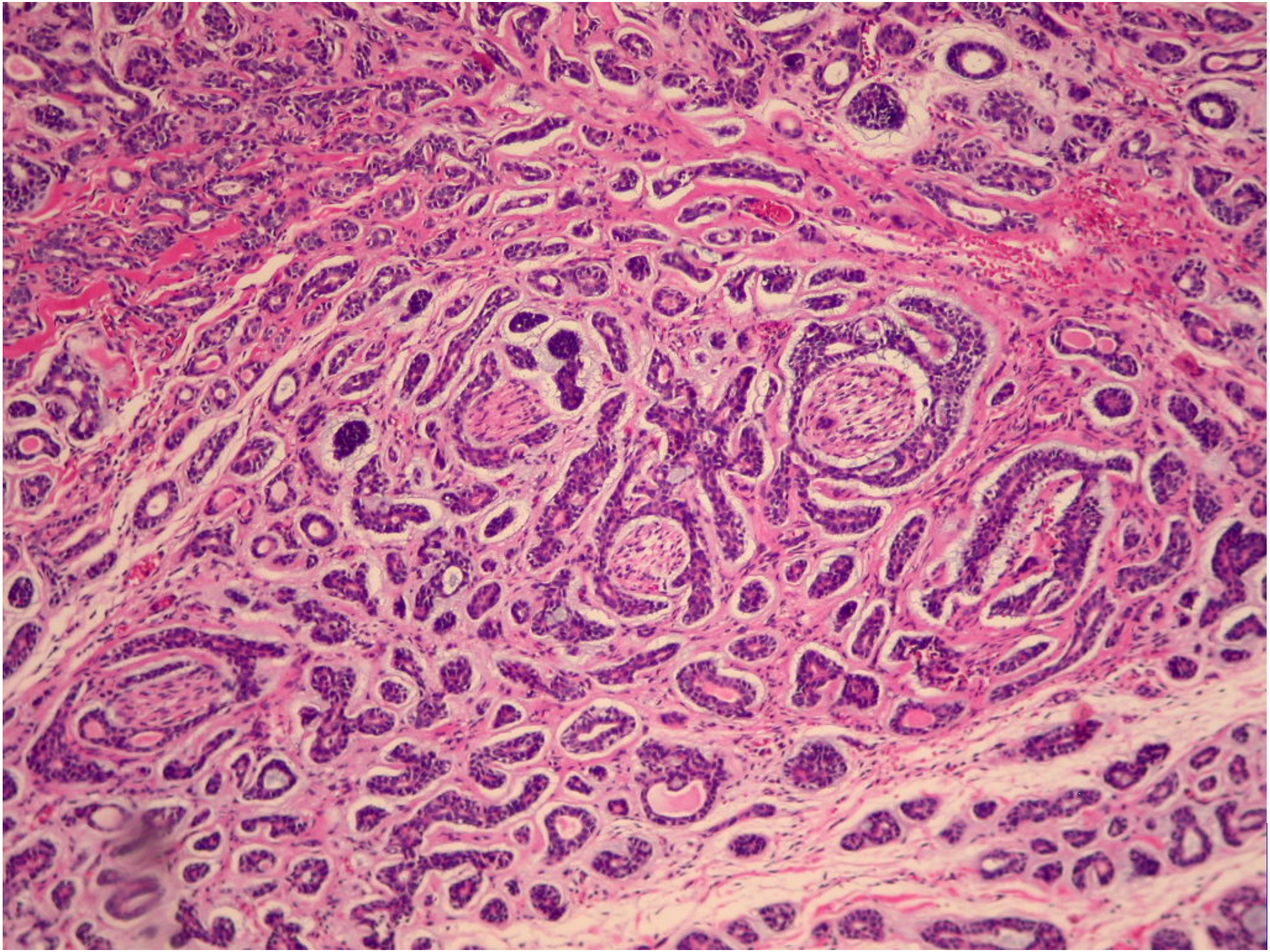
Microscopic appearance

- similar to that seen in salivary gland
- growth patterns – tubular, cribriform and solid
- Bidirectional differentiation toward luminal cells and myoepithelial cells is characteristic
- ACC is highly invasive and seldoms produces much tissue reaction.
- Perineural invasion, as elsewhere, is frequently noted
- Nuclei tend to be small, dark and angular except in the solid pattern tumors where the nuclei are larger, exhibit mild pleomorphism and more mitotic activity.









Adenoid cystic carcinoma differential diagnosis

- Primary parotid gland adenoid cystic carcinoma must be excluded clinically

Ceruminous adenocarcinoma

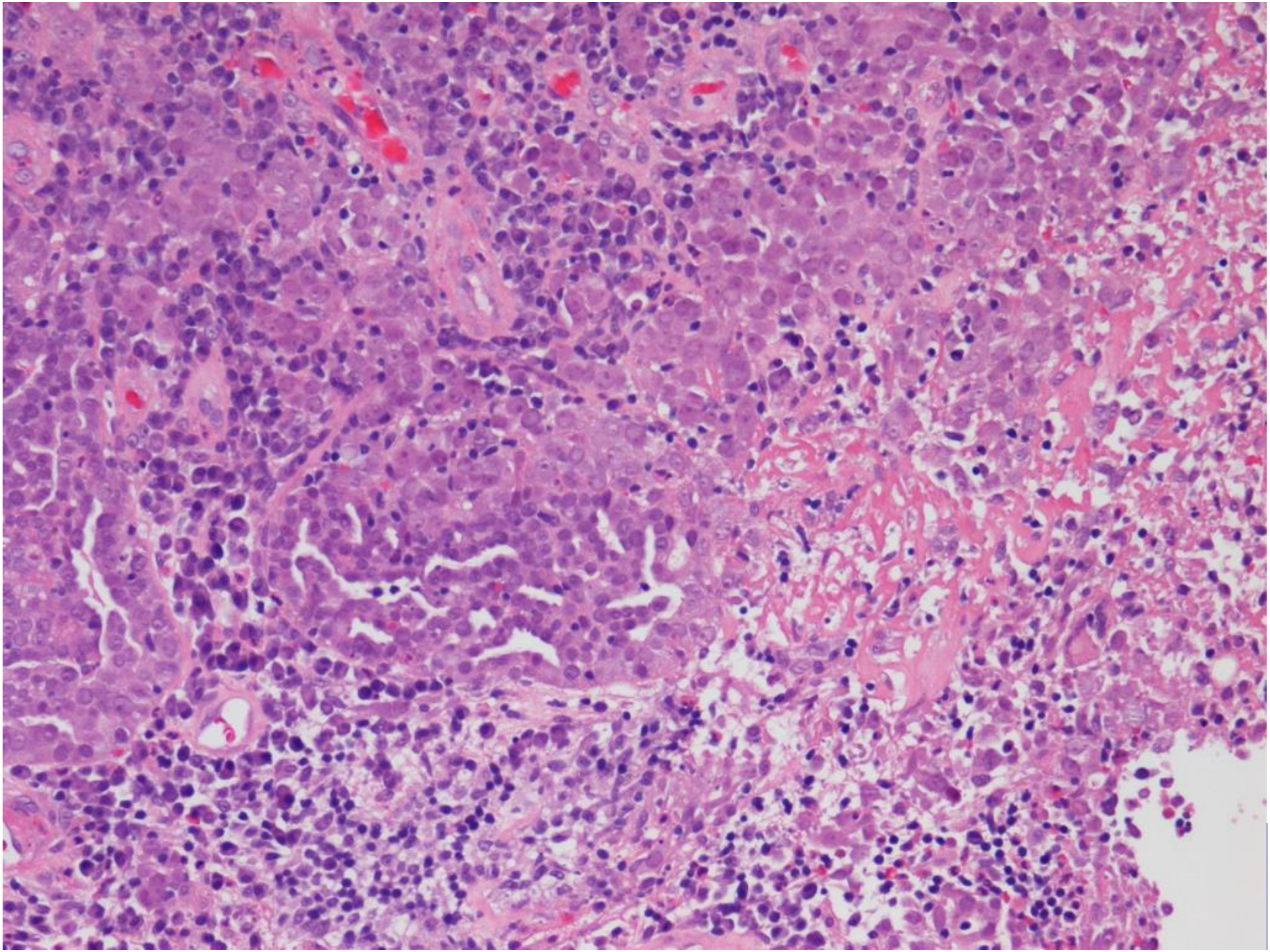
- Ceruminous adenocarcinoma is considerably less common than ACC
- may be exceptionally difficult to diagnose by light microscopy
- most are in the 5th or 6th decade
- clinical presentation does not differ significantly from ACC although pain occurs less frequently.

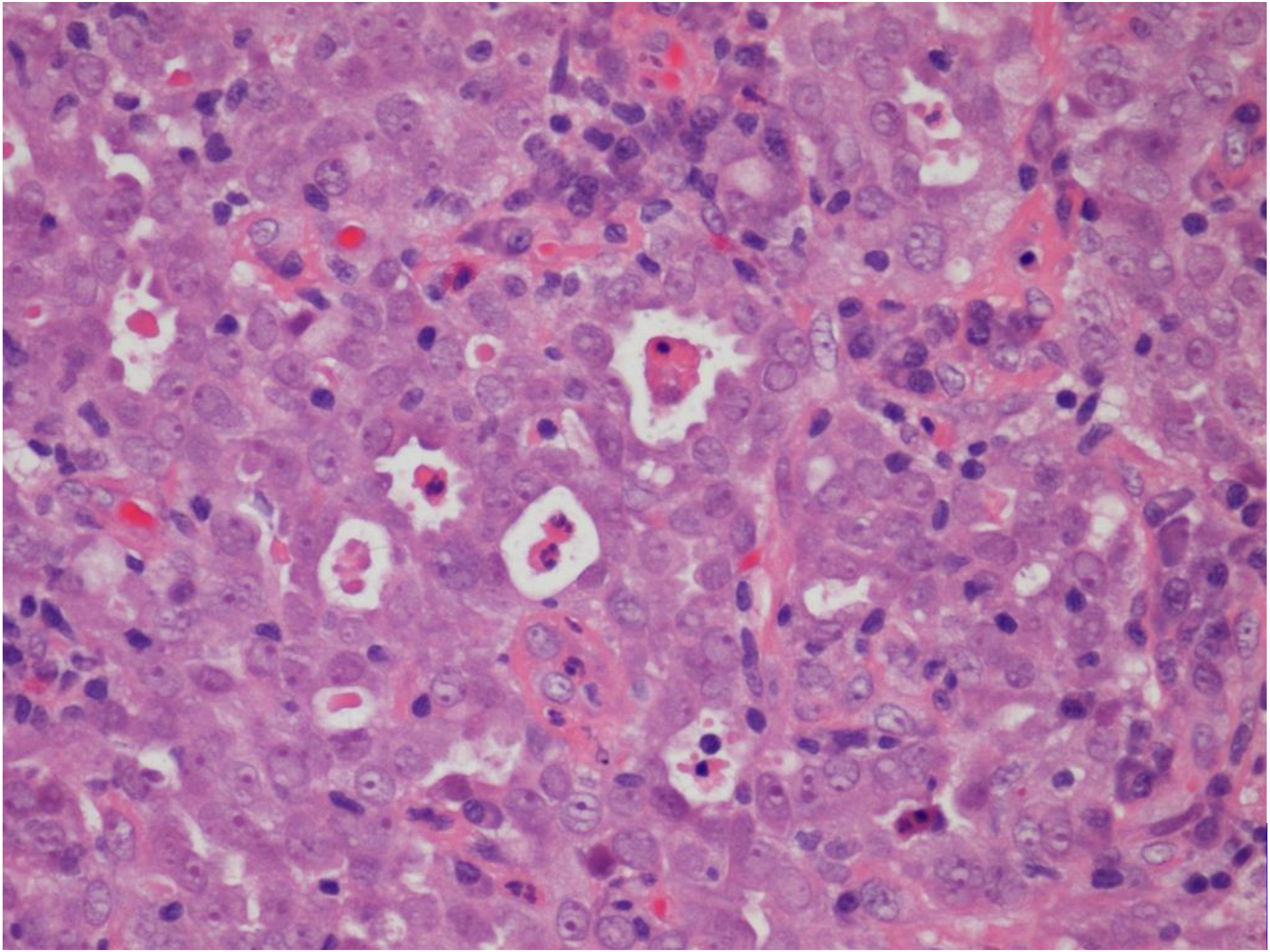
Ceruminous adenocarcinoma

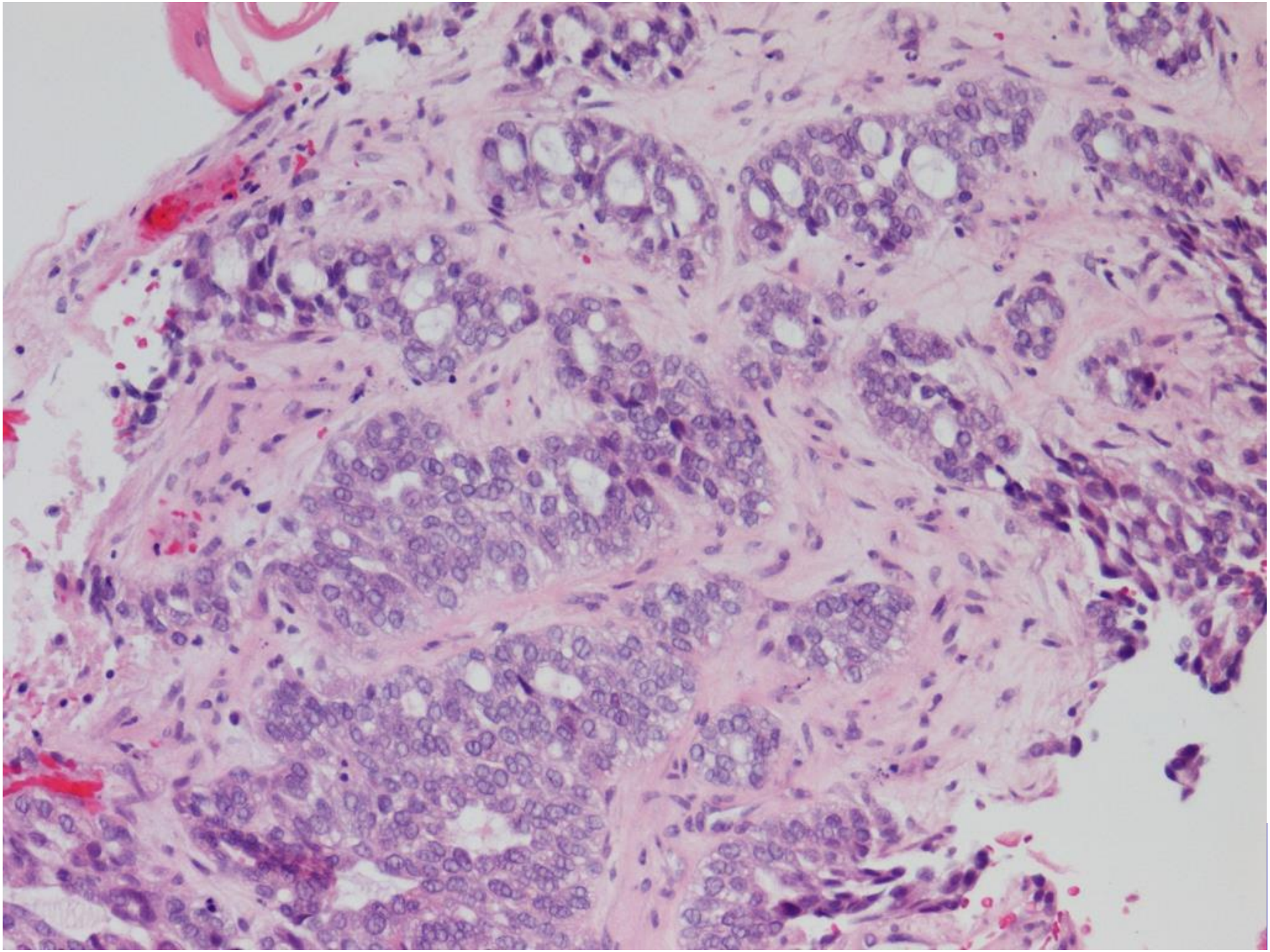
- Low-grade CAC
  - overlap morphologically with ceruminous adenoma
  - have a similar bilayered glandular architecture to CA
  - differ from CA by virtue of the presence of invasion into adjacent structures such as bone, cartilage, nerve, etc
  - may show a stromal desmoplastic response
  - differentiating low-grade CAC from CA requires an excellent biopsy that shows the relationship of the tumor with the surrounding tissue.

Ceruminous adenocarcinoma

- High grade CAC
  - lack the bilayered glandular morphology of CA, instead showing more complex glandular architecture
  - nuclear pleomorphism, mitotic activity ++







Malignant ceruminous gland neoplasms

- Primarily surgical treatment
  - Radical resection
- Adjuvant radiotherapy often required
- Prognosis: poor

Neoplasms of the middle ear and temporal bone

- Paraganglioma
- Middle ear adenoma
- Endolymphatic sac tumor
- Squamous cell carcinoma
- Metastatic tumor
- Others

Middle ear adenoma/carcinoid

- First descriptions of middle ear glandular neoplasms described as adenomas in 1976
- Massachusetts Eye and Ear Infirmary described an indistinguishable tumor as a carcinoid tumor in 1980
- Since that time there have been a number of reports describing these tumors by a variety of names
  - carcinoid tumor
  - middle ear adenoma
  - adenomatous tumor of the middle ear
  - adenocarcinoid
  - amphicrine tumor
- Recently, Torske and Thompson suggested that neuroendocrine adenoma of the middle ear might be the best designation.
- Middle ear adenoma is the most widely accepted name

Middle ear adenoma/carcinoid

	Middle ear adenoma Torske KR, Thompson LD 2002 (n=48)
Males	27
Females	21
Range	20-80
Mean	45
Hearing loss	69%
ME mass	25%
EAC extension	4%
Size (range)	02-3.0 cm
Size (mean)	0.8 cm
Recurrence	21%
Metastasis	0

Middle ear adenoma/carcinoid

- Typically described intraoperatively as an avascular, rubbery unencapsulated mass
- Surgeons readily recognize that they are not dealing with a paraganglioma once they have exposed the tumor, even though that is the usual preoperative diagnosis – lack of vascularity

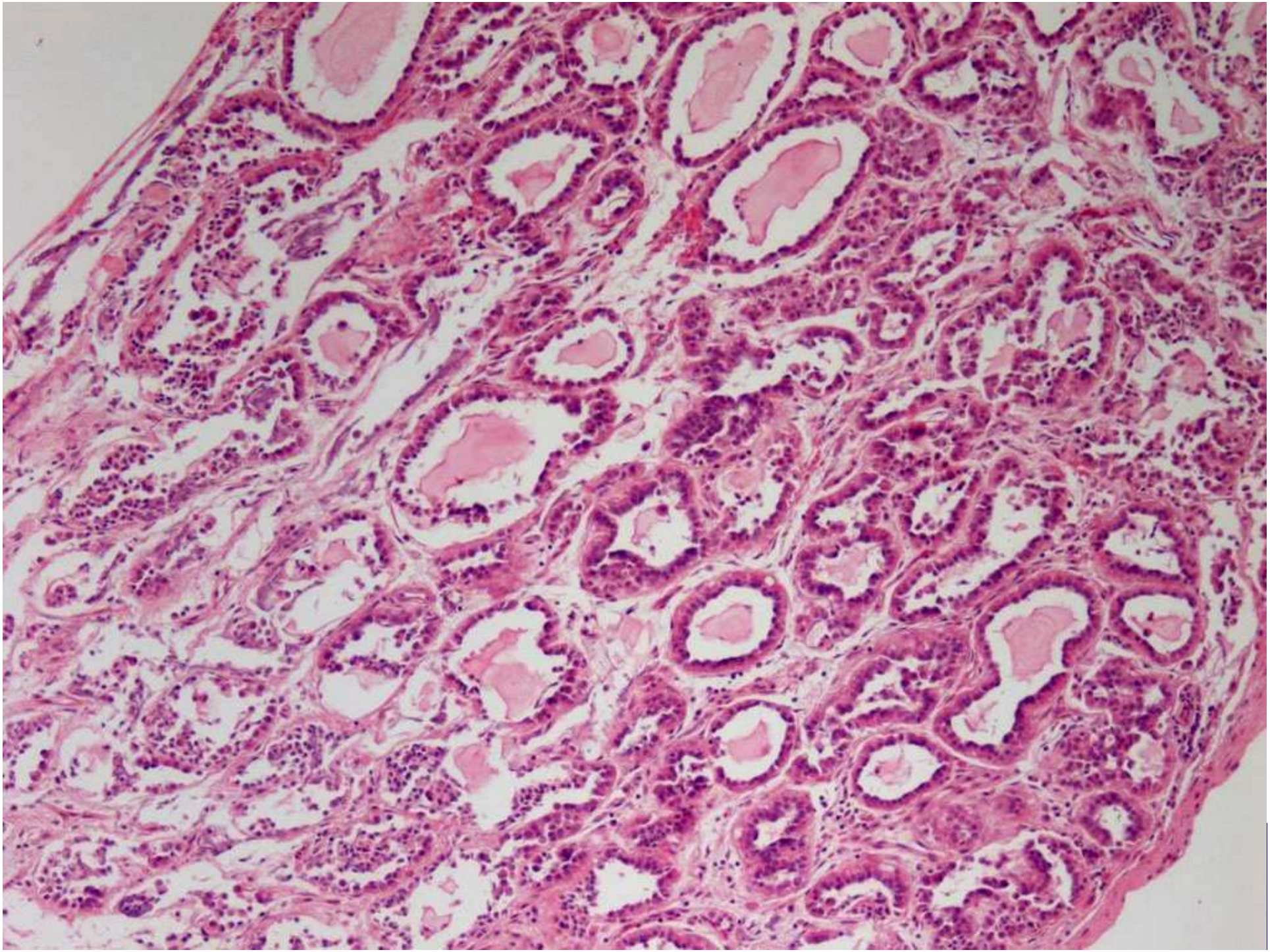
Middle ear adenoma/carcinoid

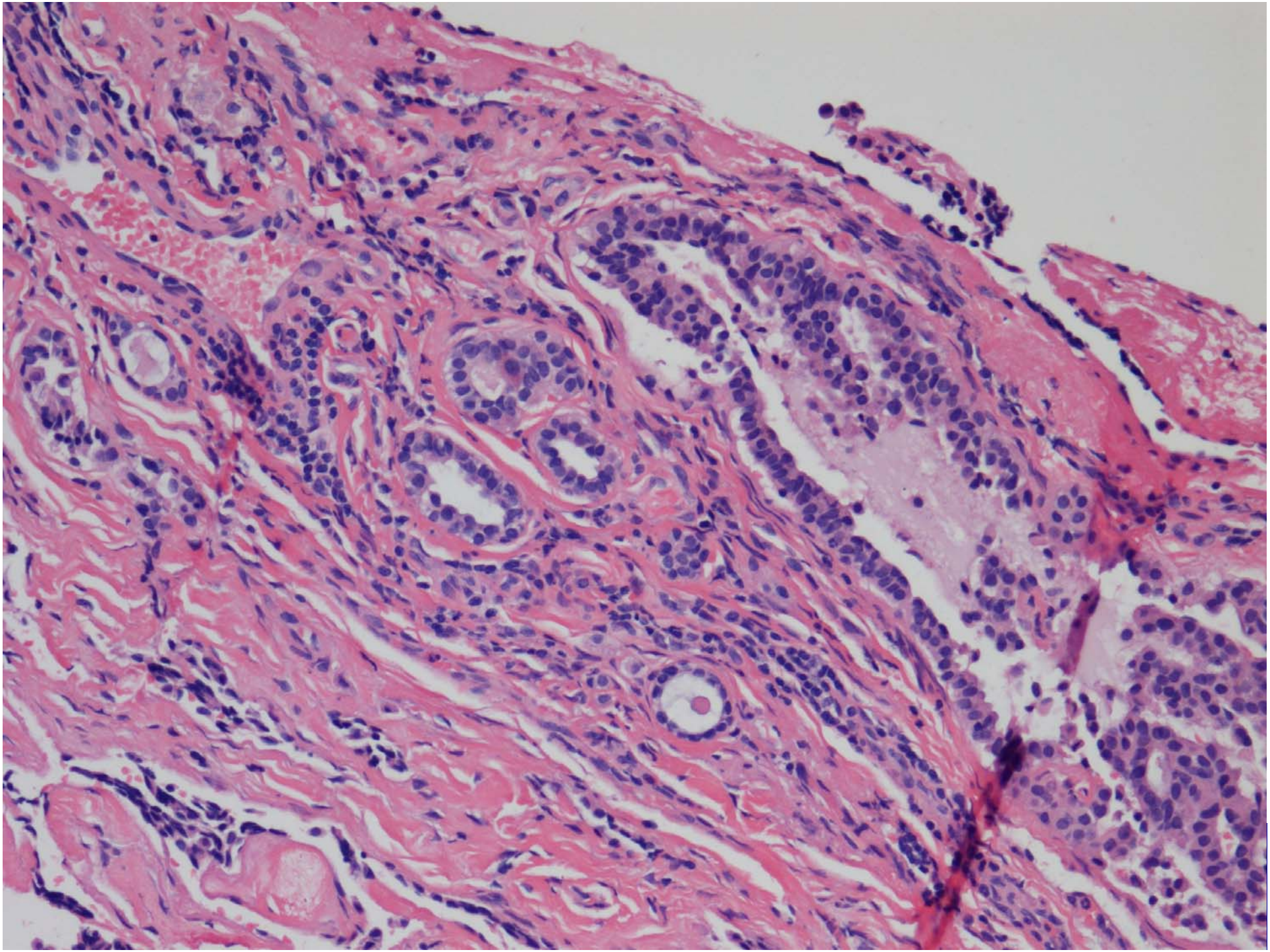
Variable architectural patterns:

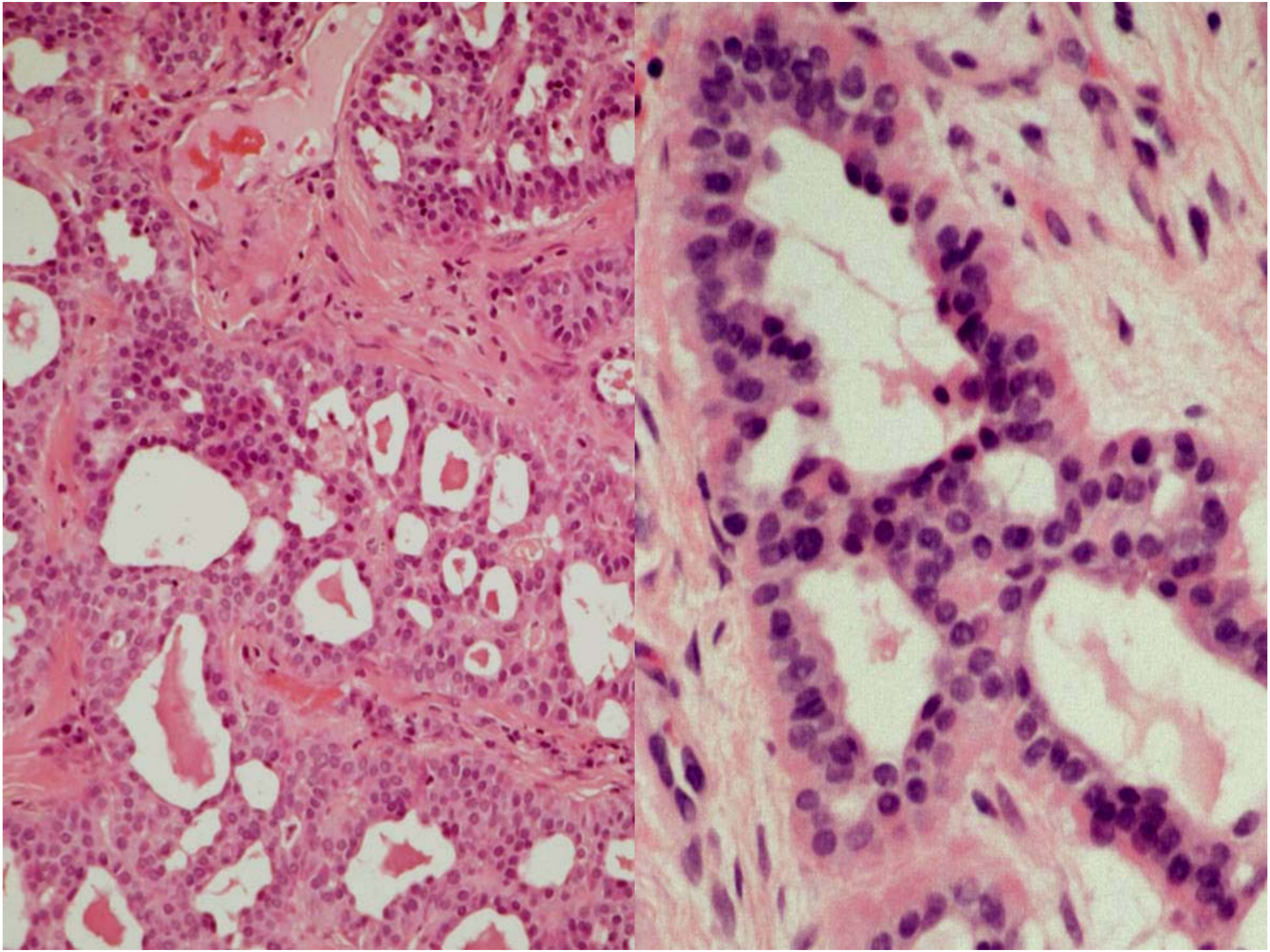
- Glandular
  - well-formed glands lined by a single layer of cells without a myoepithelial layer
  - back to back
- Trabecular
  - Trabeculae are commonly composed of cuboidal to low columnar cells surrounded by paucicellular fibrous tissue
- Solid
- Many tumors have an infiltrative appearance with small nests or cords of cells embedded in a fibrous stroma
- Perineural invasion in a minority

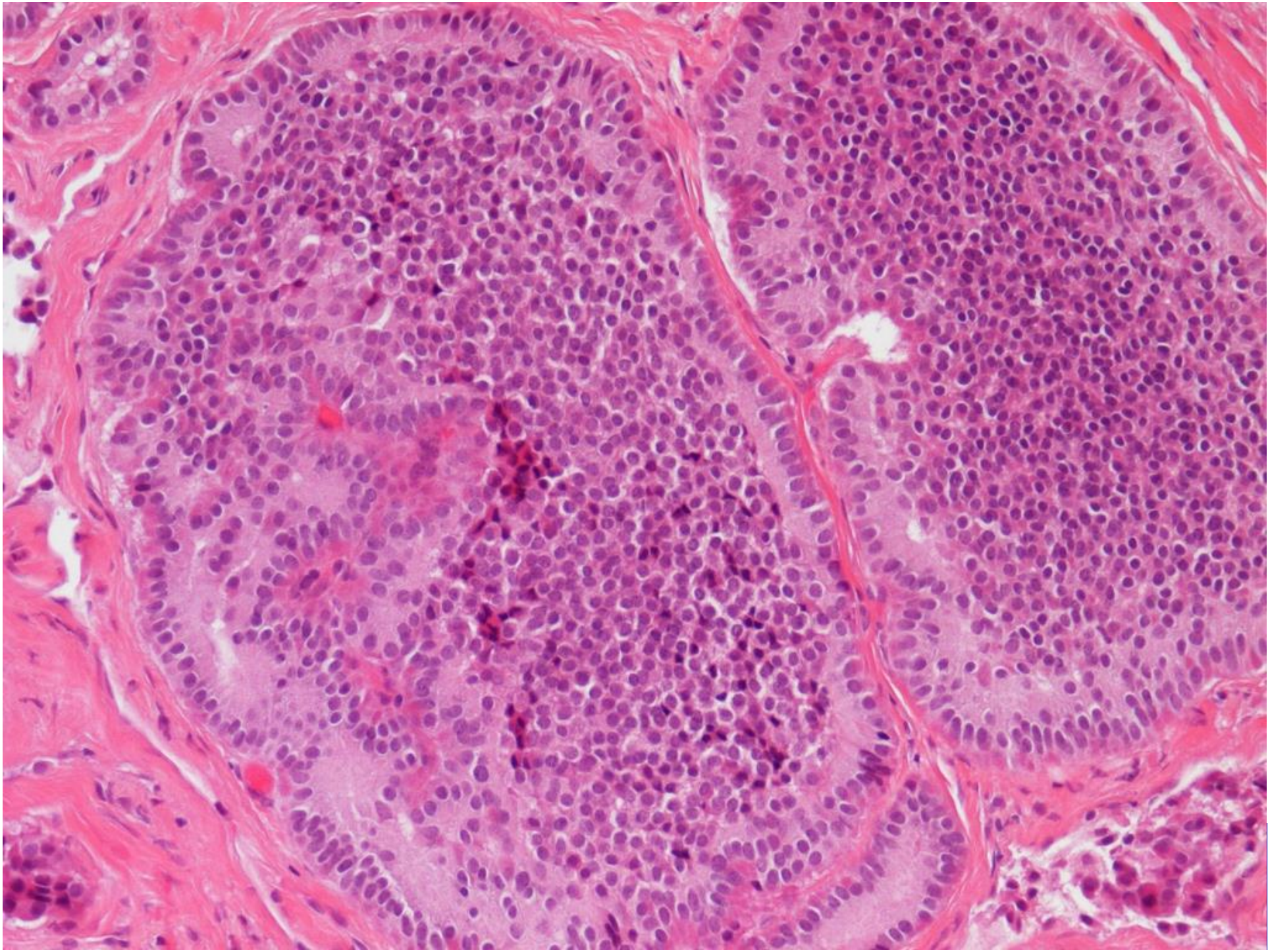
Middle ear adenoma/carcinoid

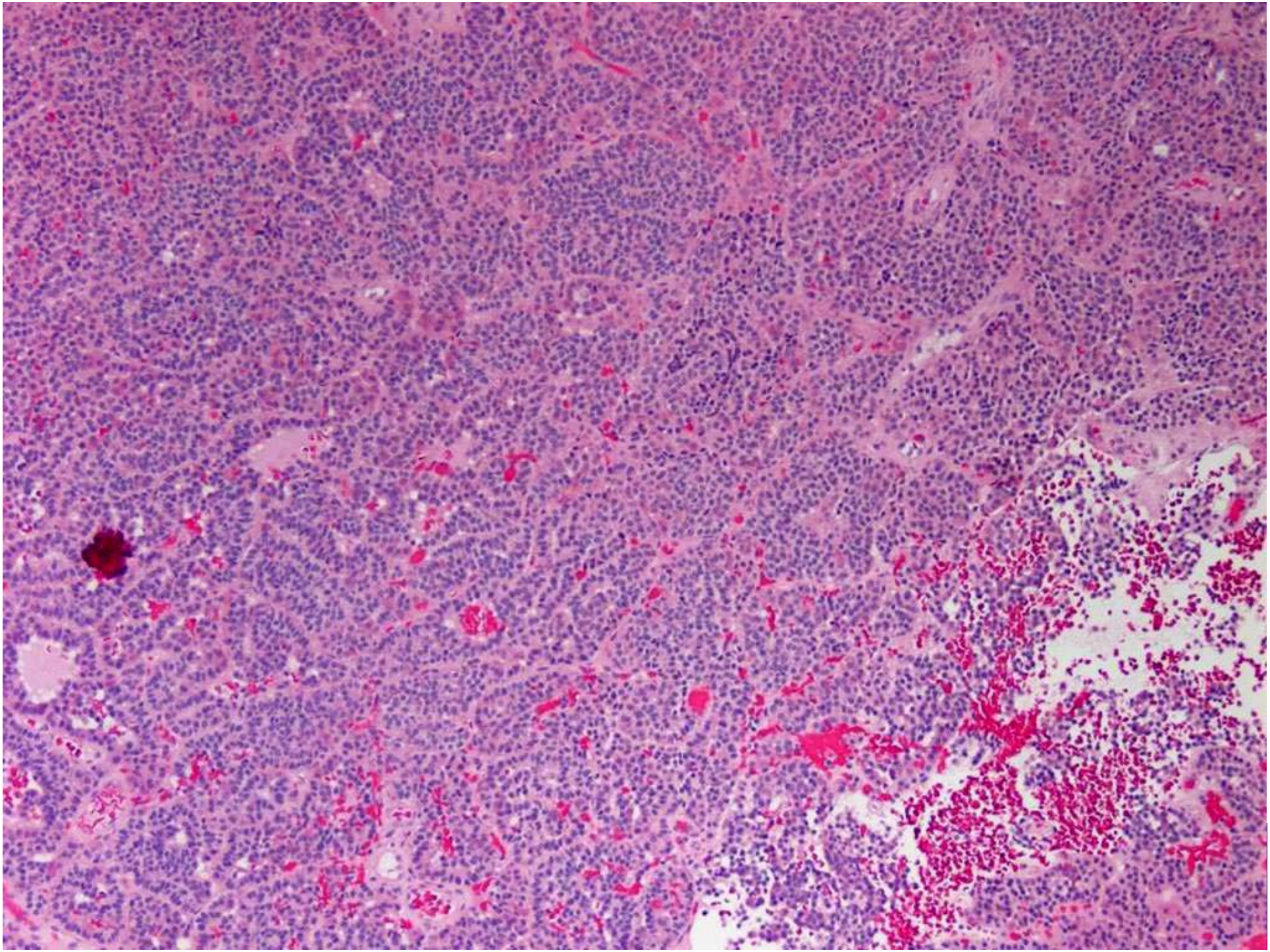
- Cuboidal cells with a moderate amount of eosinophilic, sometimes granular, cytoplasm
- Frequently, these cells have a plasmacytoid appearance
- Nuclei are typically uniform, oval to round and may show a salt and pepper chromatin pattern with inconspicuous or absent nucleoli
- Mitoses are absent
- Rarely mild to moderate nuclear pleomorphism.

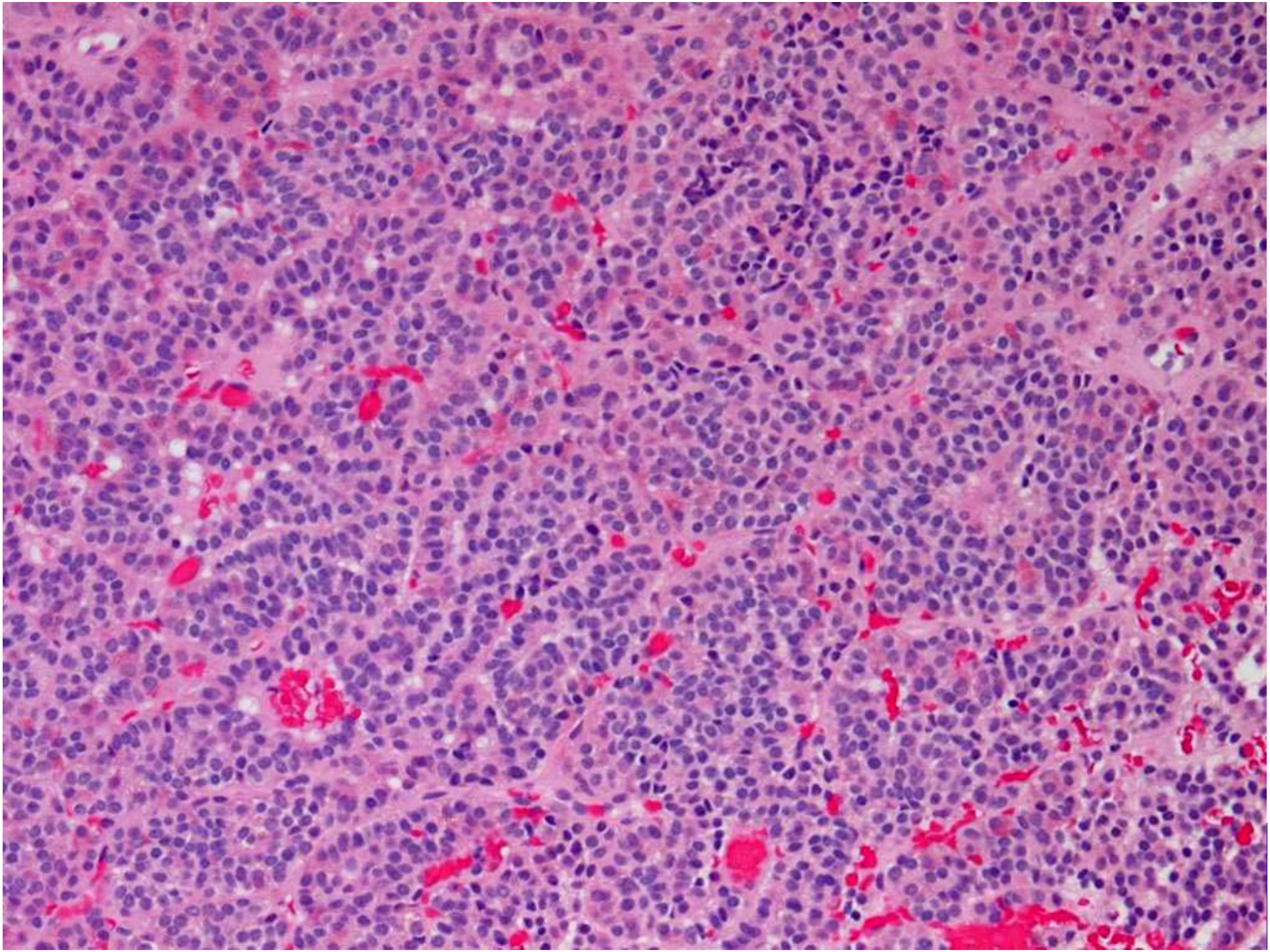


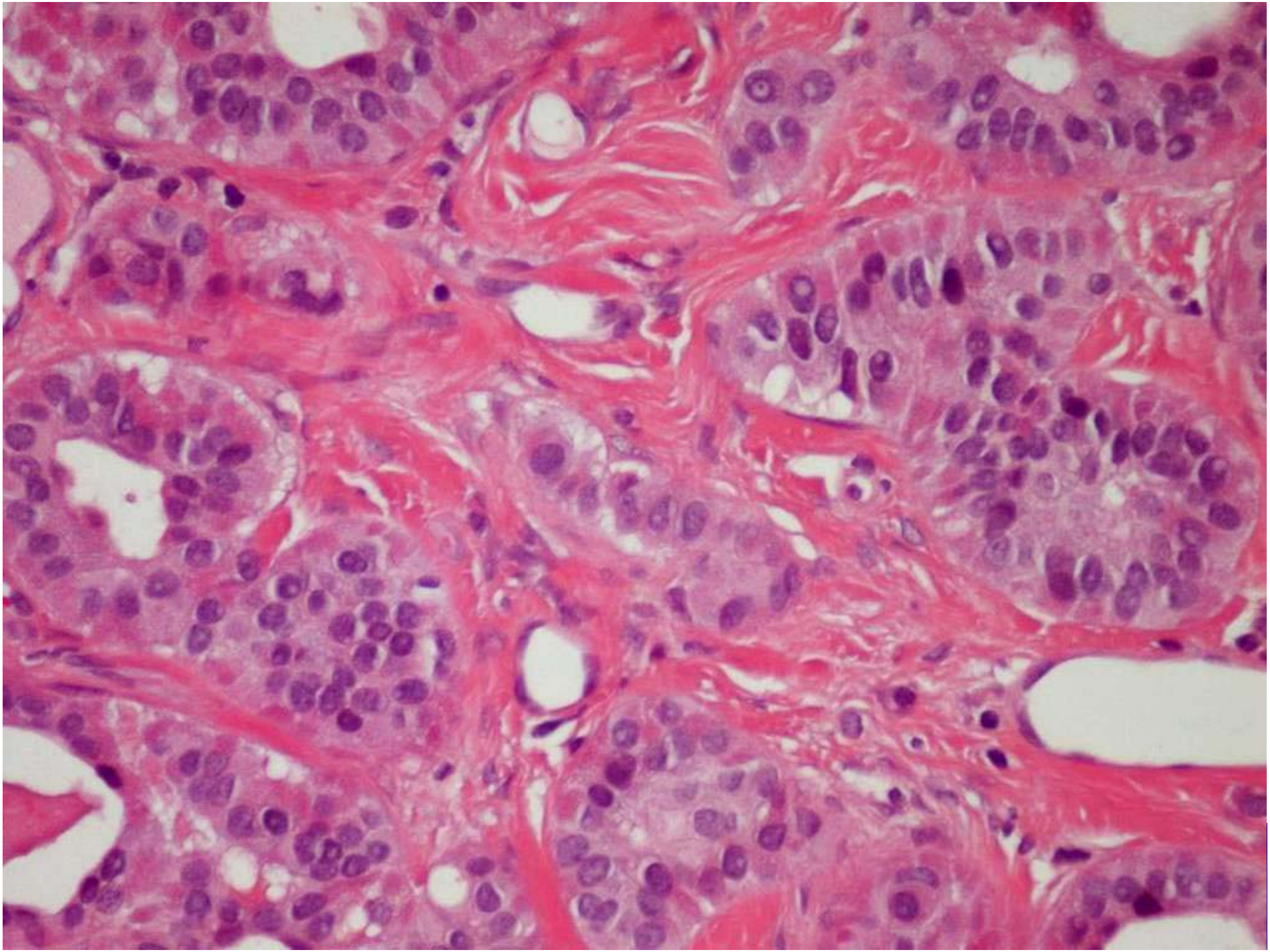


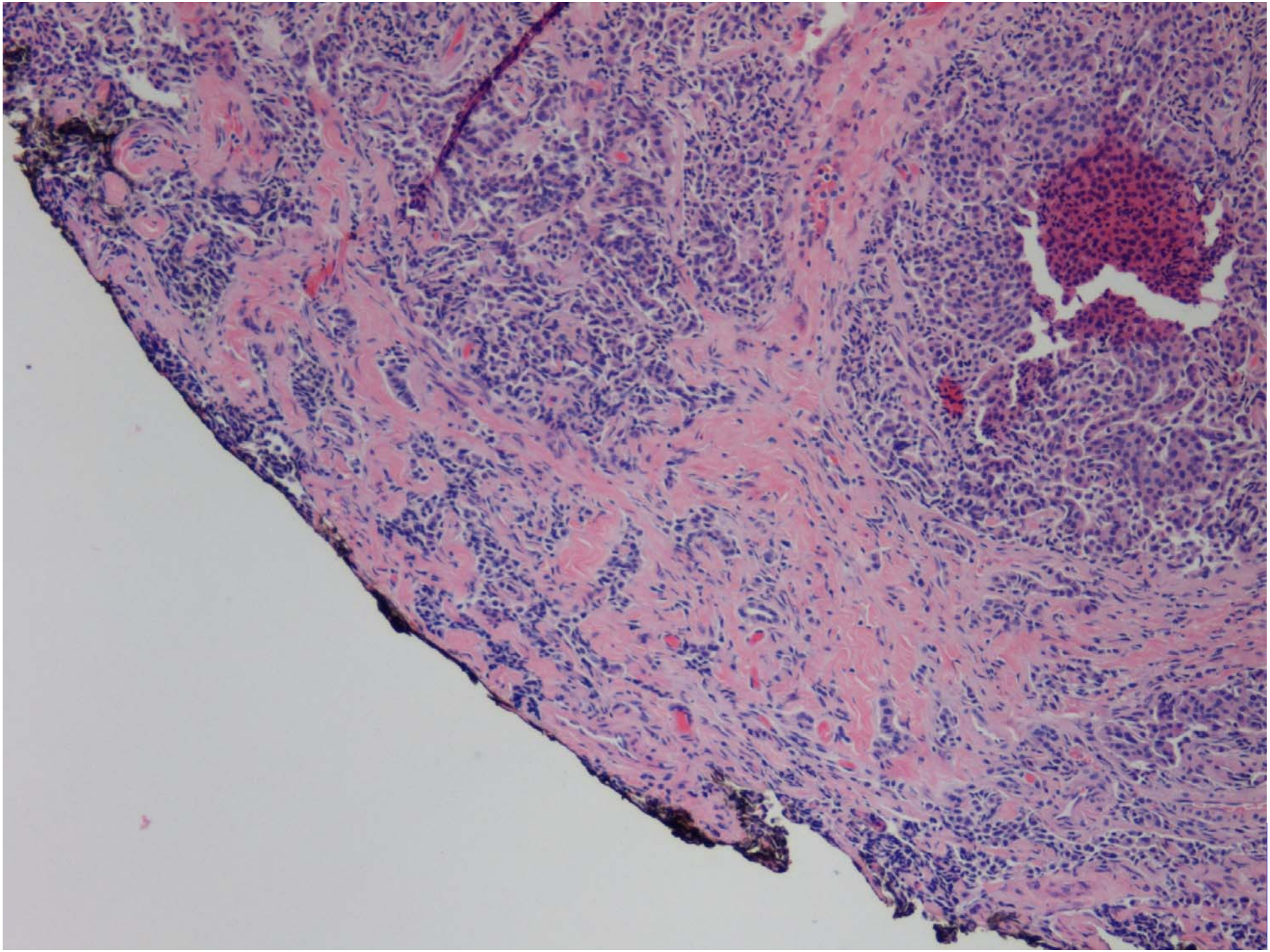


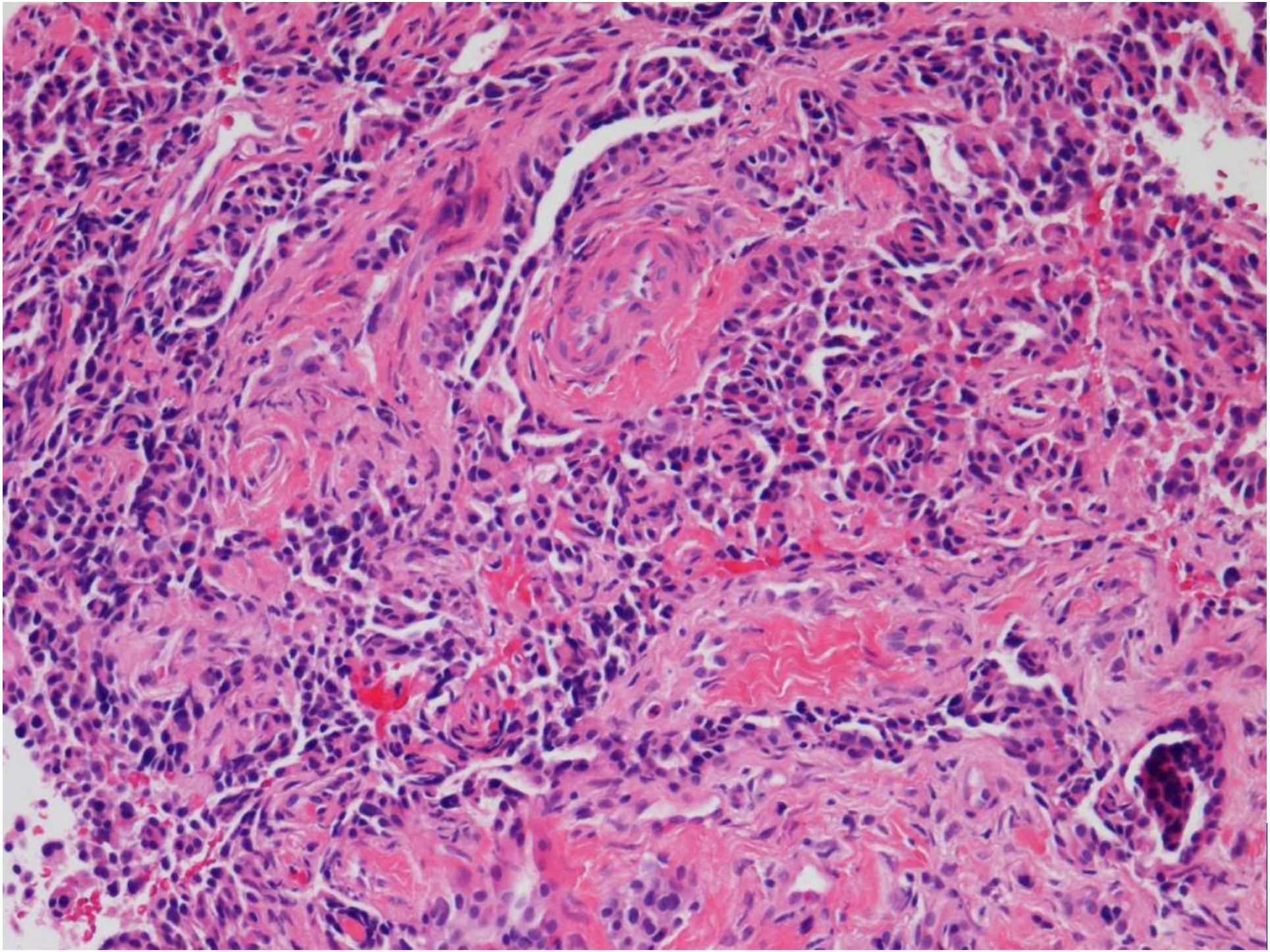


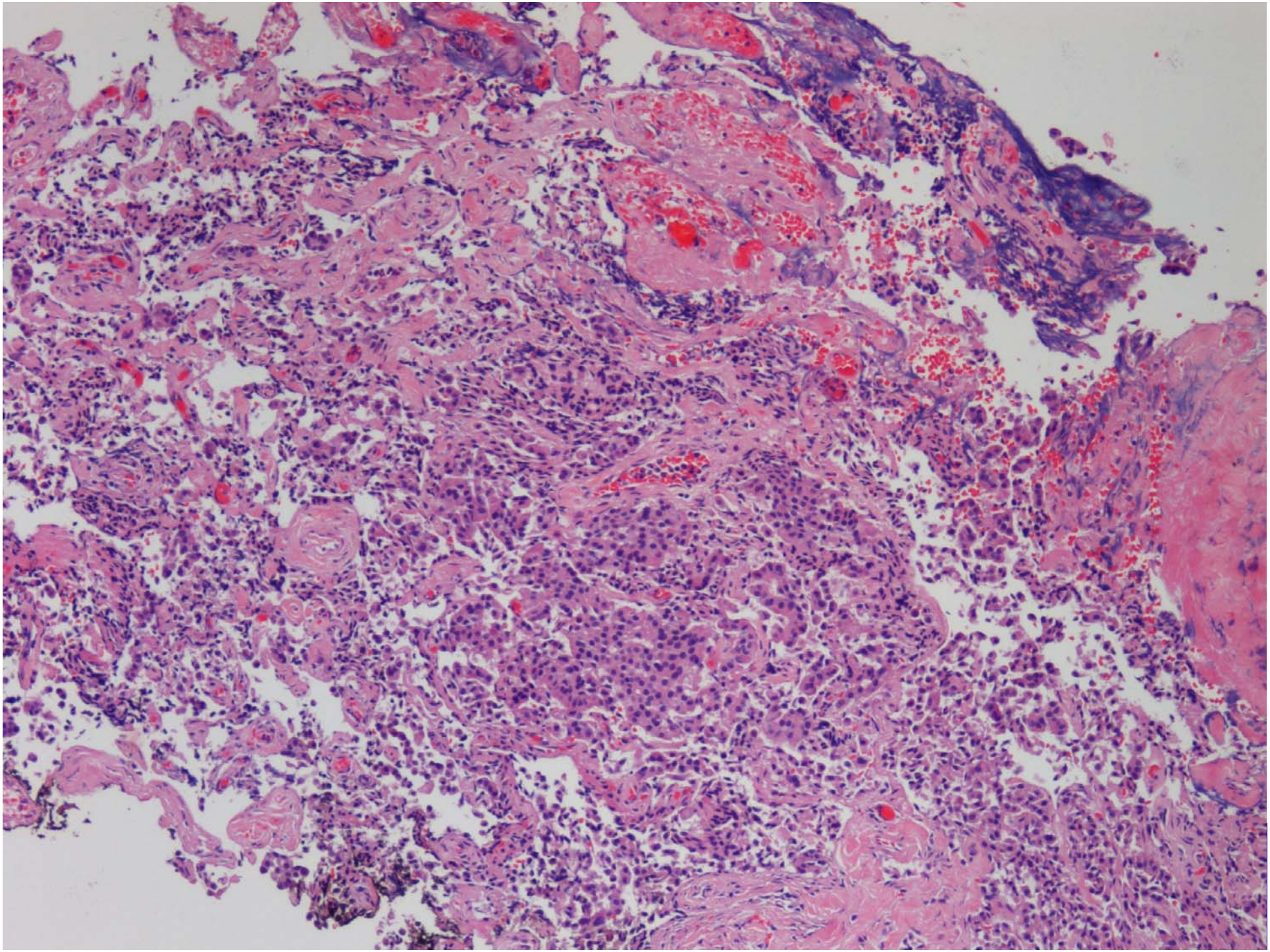


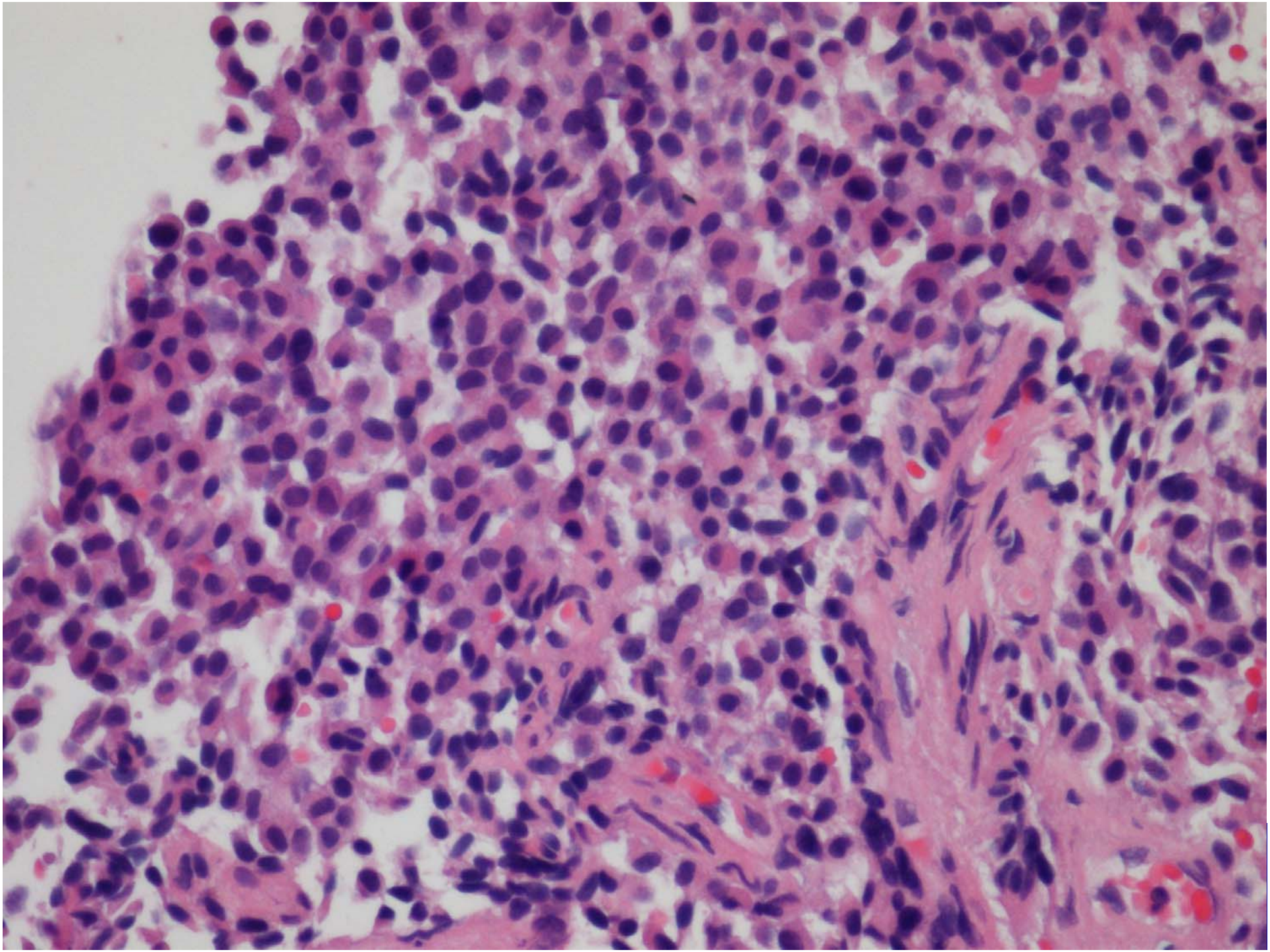


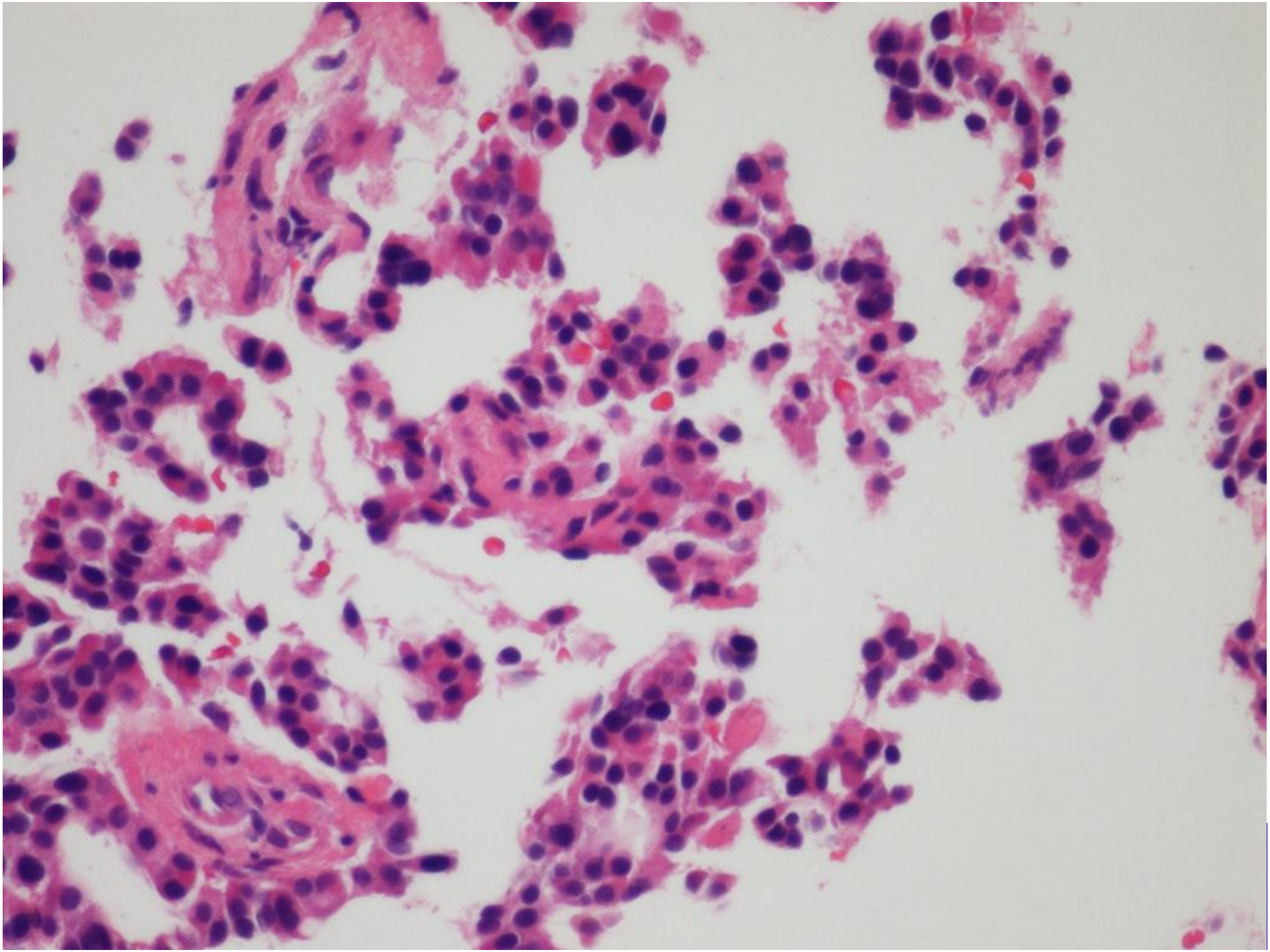


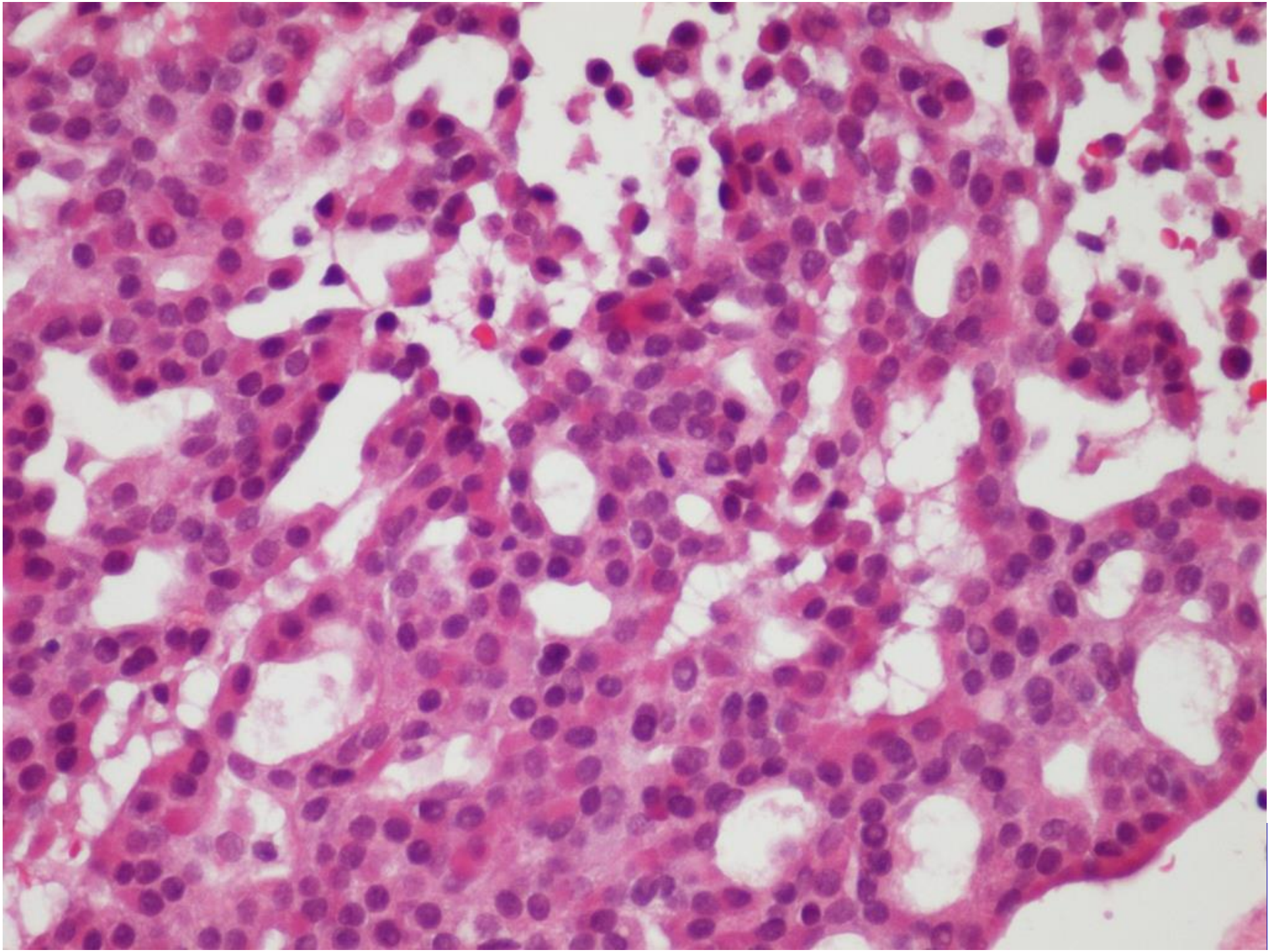


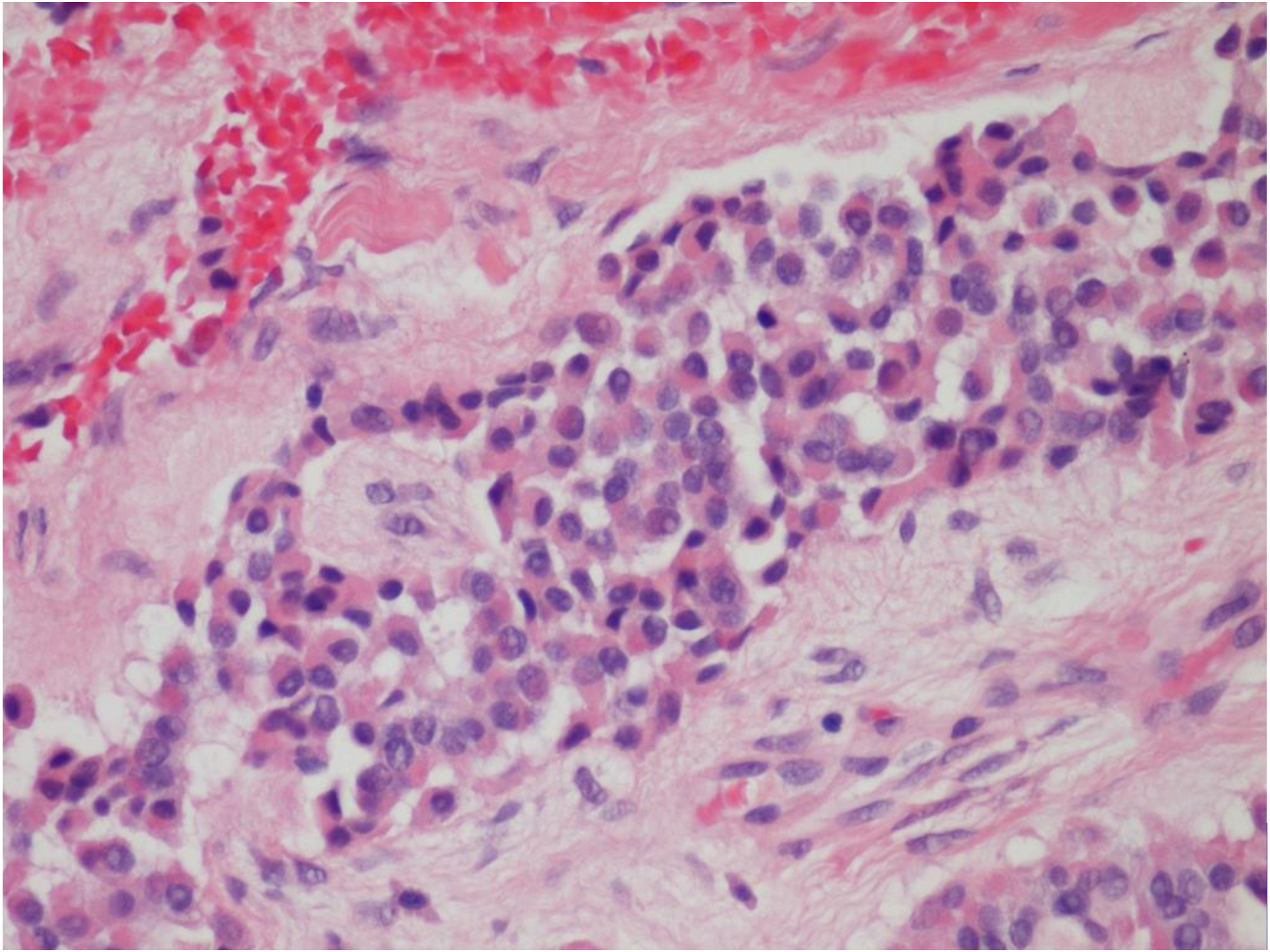


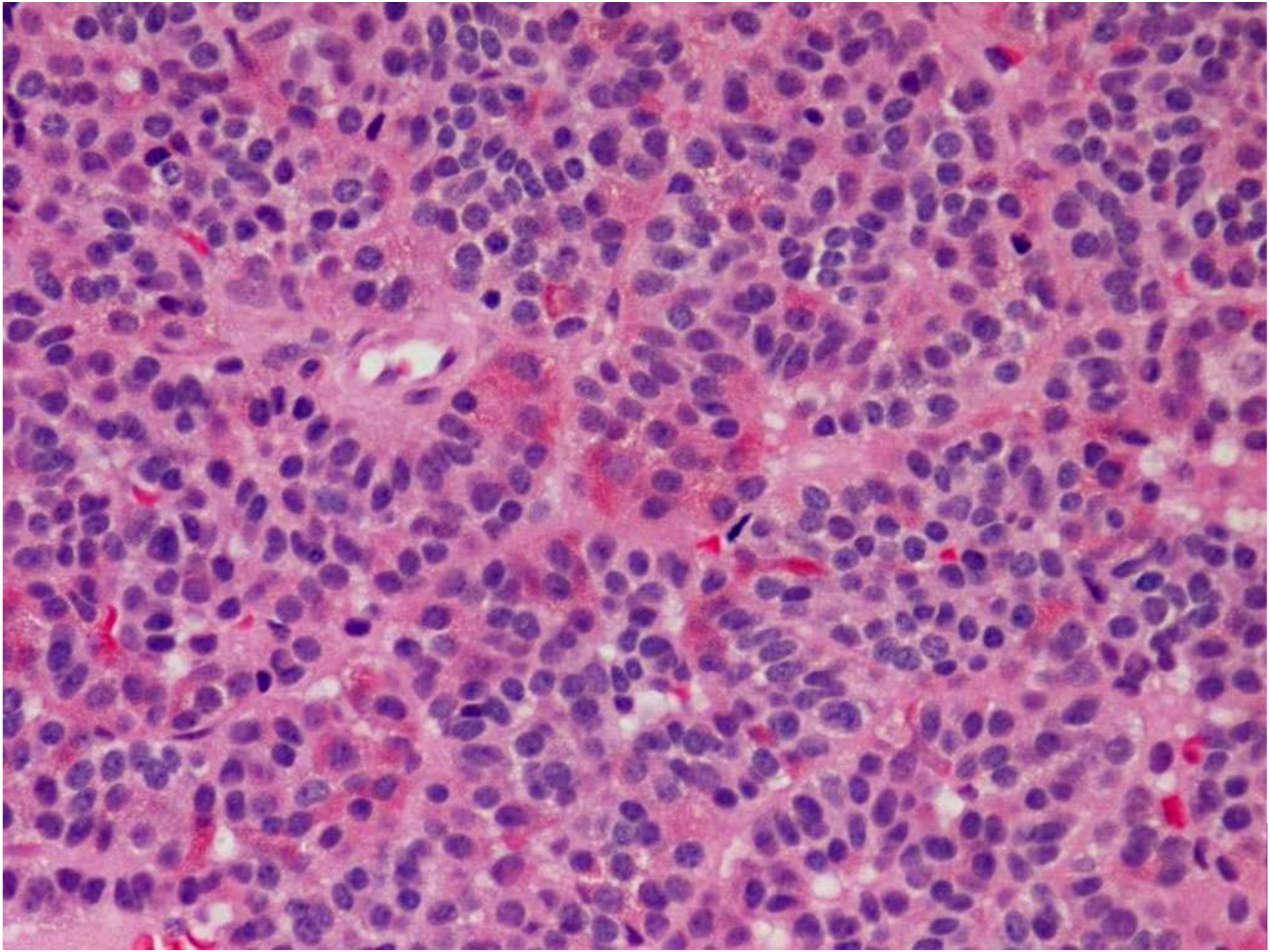


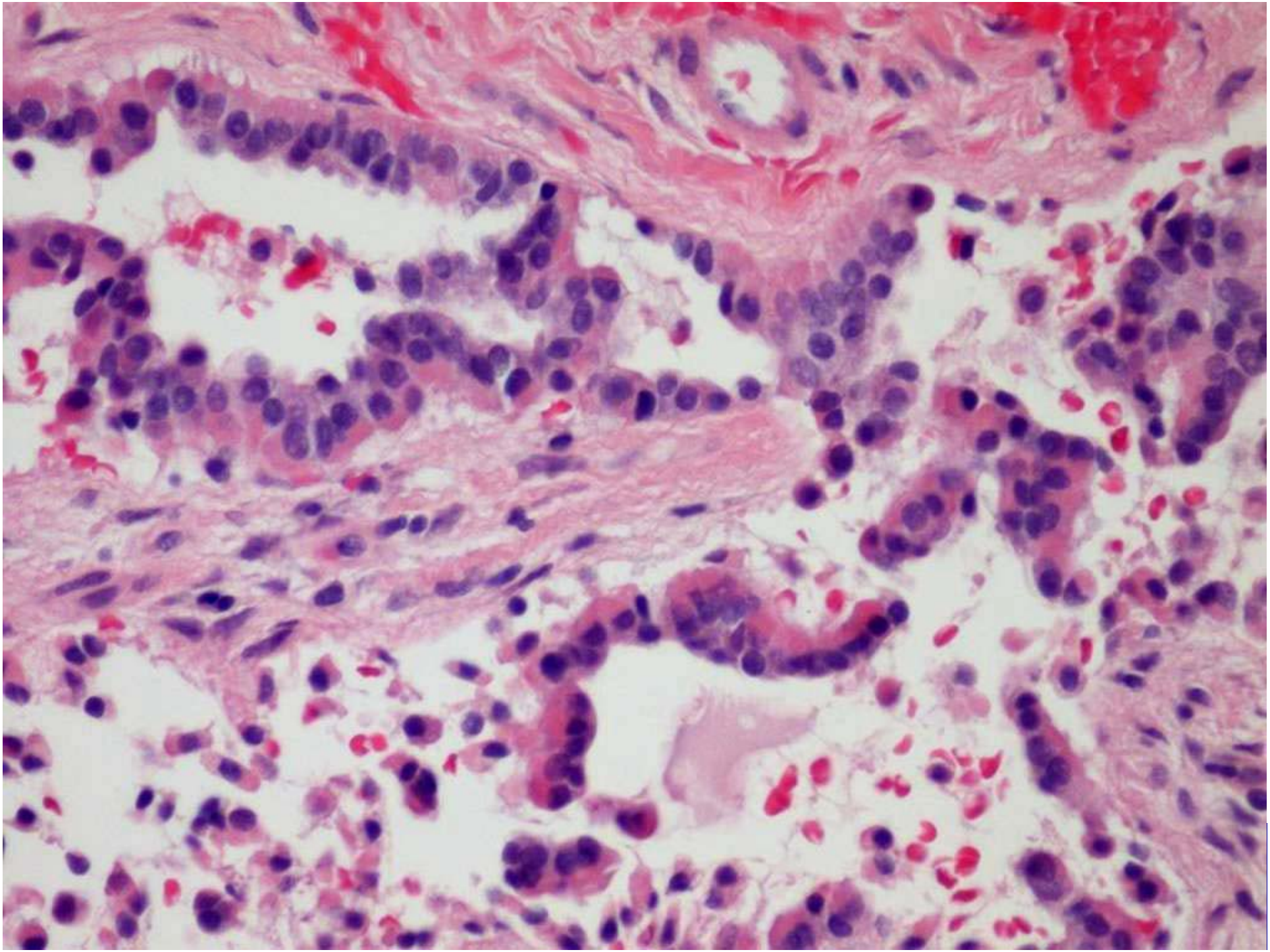








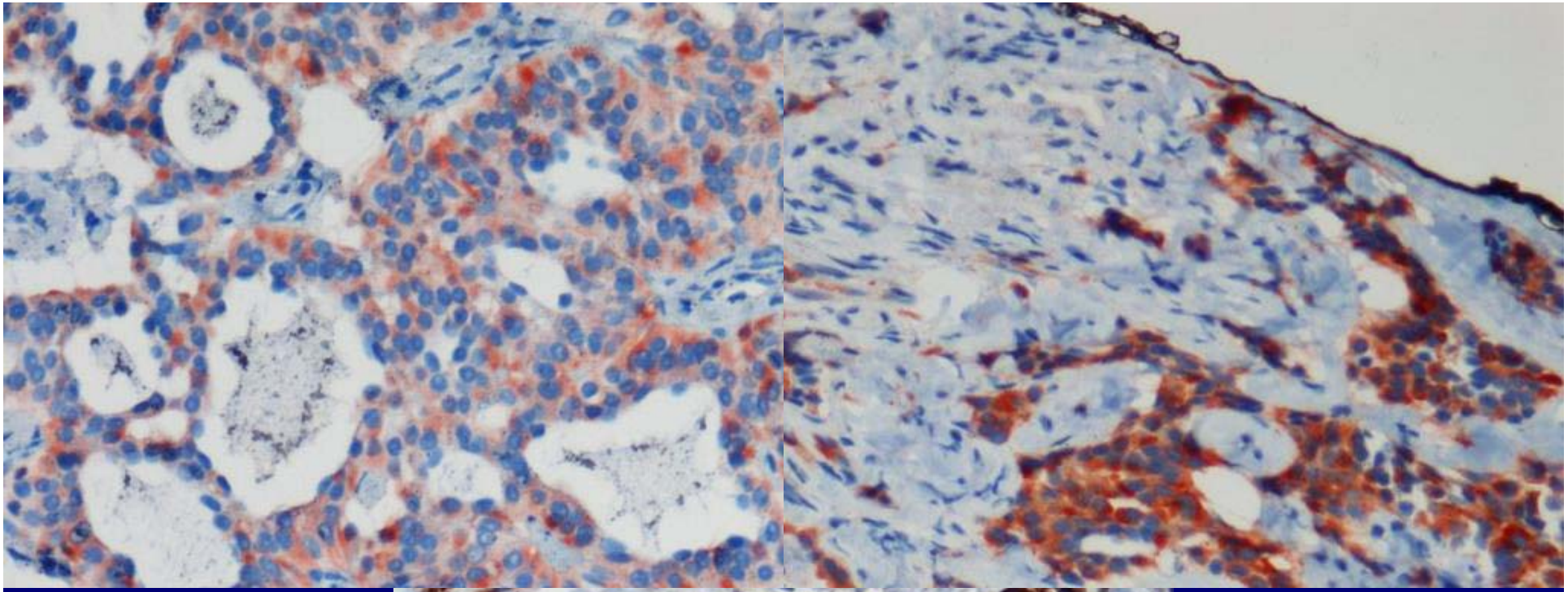


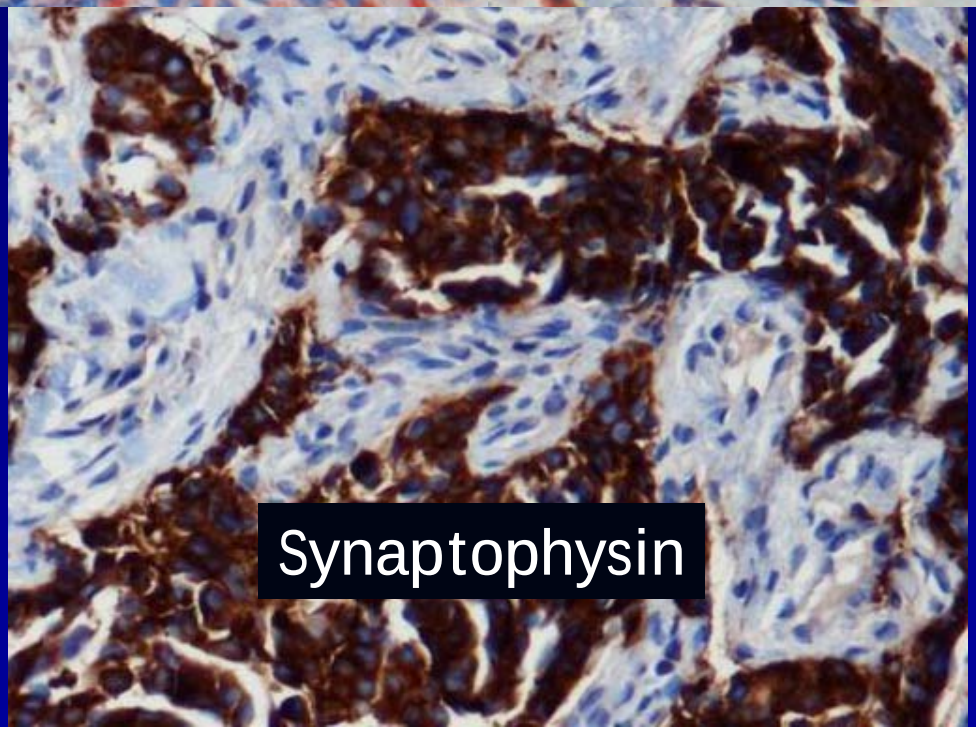


Middle ear adenoma/carcinoid

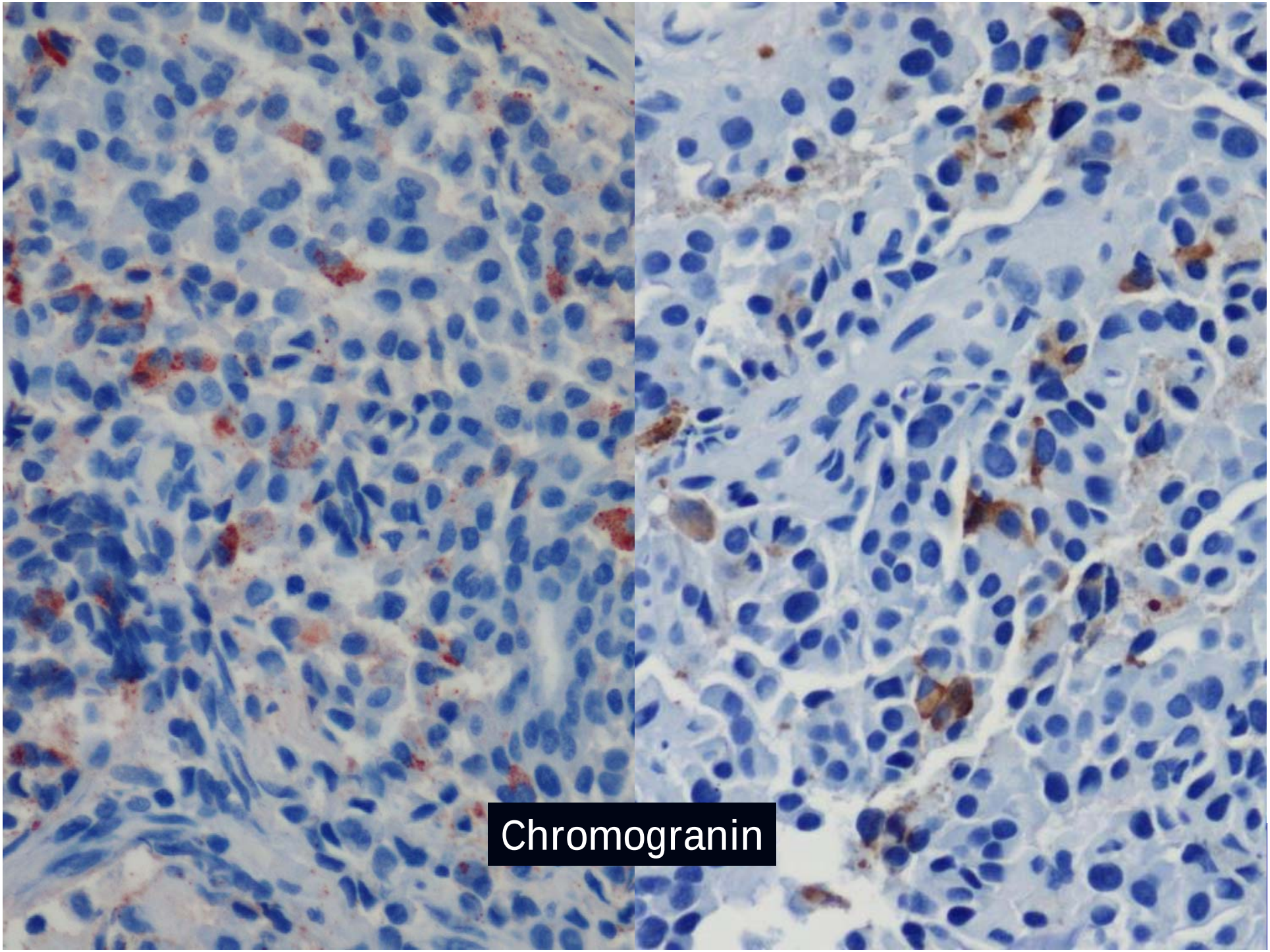
Immunohistochemistry

- pan-keratin or CAM5.2 positivity
- One or more neuroendocrine markers are positive in the vast majority
  - chromogranin
  - synaptophysin
  - neuron-specific enolase
  - serotonin





Synaptophysin


Chromogranin

Middle ear adenoma/carcinoid Differential diagnosis

- Endolymphatic sac tumor
  - MEA/C lacks papillary architecture and follicle like spaces
  - Neuroendocrine differentiation is seen in MEA/C
- Metastatic adenocarcinoma
  - bland and uniform cytologic features of MEA/C
- Glandular metaplasia/hyperplasia in chronic otitis media
  - lacks plasmacytoid cells
  - lacks neuroendocrine differentiation
  - associated with a chronic inflammatory reaction.

Middle ear adenoma/carcinoid

	Middle ear adenoma Torske KR, Thompson LD 2002 (n=48)	**Carcinoid tumor** Ramsey MJ, et al. 2005 (n=46)
Males	27	27
Females	21	19
Range	20-80	16-72
Mean	45	43
Hearing loss	69%	87%
ME mass	25%	78%
EAC extension	4%	20%
Size (range)	02-3.0 cm	N/A
Size (mean)	0.8 cm	N/A
Recurrence	21%	22%
Metastasis	0	9%

Middle ear adenoma/carcinoid

- In 2002 there had been a single case report of metastasis to cervical lymph node in a patient with middle ear carcinoid
  - post-radiotherapy
- Now three additional reports of metastatic "carcinoid tumor"
  - in all three of these cases, tumor metastasized to intraparotid lymph nodes
  - local recurrence was also noted in all 4 cases with metastatic tumor

Middle ear adenoma/carcinoid

- Until this controversy is resolved:
  - use the terminology middle ear adenoma/carcinoid (with explanatory note)
  - instruct the clinicians that rare cases of middle ear adenoma have metastasized

Endolymphatic sac tumor

Synonyms for papillary tumors of middle ear/temporal bone
Endolymphatic sac (papillary) tumor
Adenoma of endolymphatic sac
Adenoma/Adenocarcinoma of temporal bone or mastoid
Low-grade adenocarcinoma of probable ELS origin
Papillary adenoma of temporal bone
Aggressive papillary middle ear tumor
Heffner tumor

Labrynthine anatomy

- The bony labyrinth is divided into three portions:
  - Vestibule
  - Semicircular canals

  } Responsible for balance

  - Cochlea

  Responsible for hearing

- Membranous labyrinth is suspended within the bony labyrinth
- Endolymphatic duct is an extension of the membranous labyrinth
- Endolymphatic duct terminates in the endolymphatic sac - partially within the petrous portion of the temporal bone, and partially within the dura in the cerebellopontine angle

Endolymphatic sac

- role in the regulation of fluid and ion balance within the inner ear
- maintenance of endolymphatic pressure
- may also play a role in the immune system.
  - Secretory IgA is found in the epithelium of the ELS.

Endolymphatic sac tumor

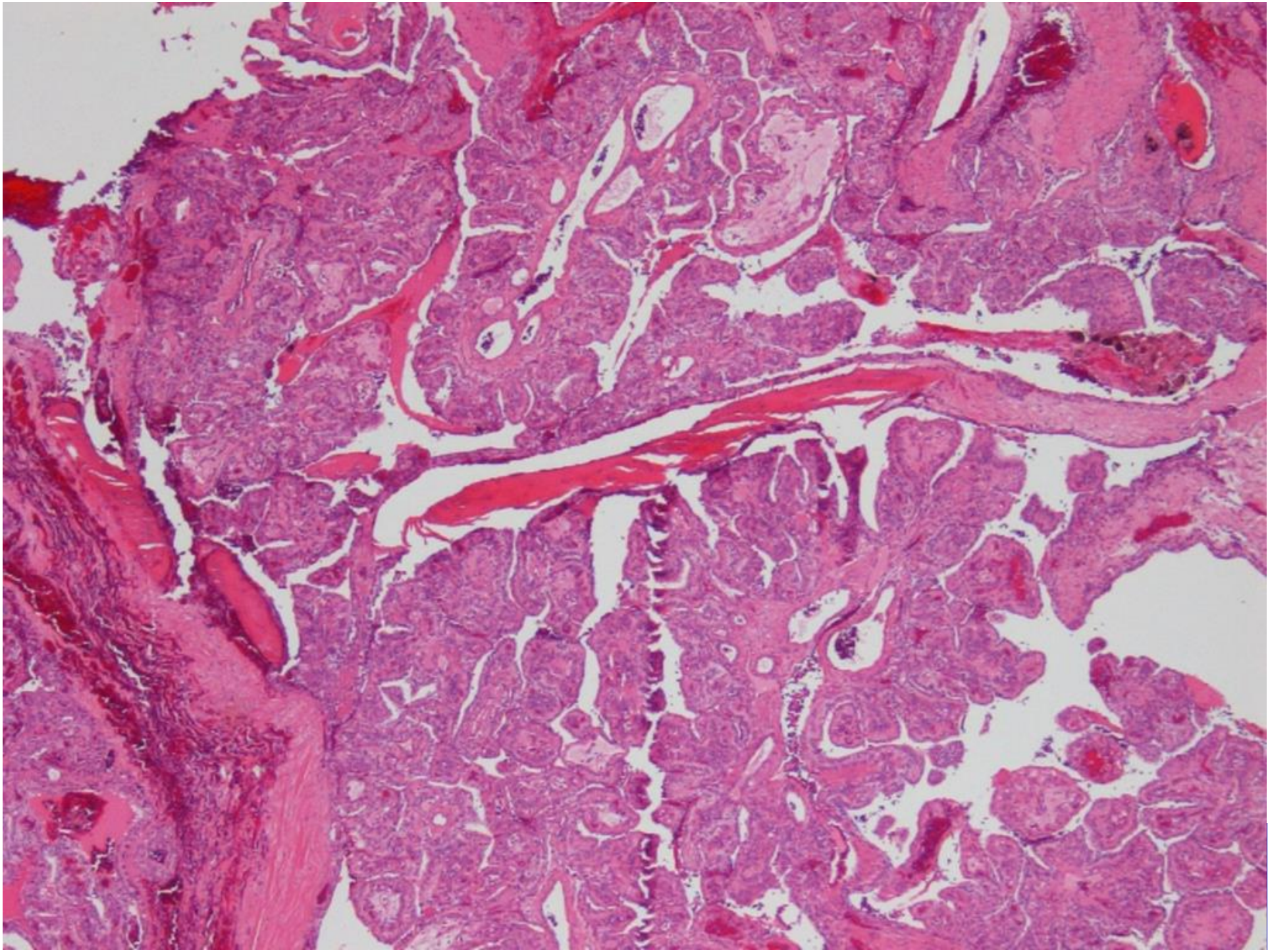
- occurs in all age groups; median age of approximately 40 years
- slight female predominance
- most prevalent presenting symptoms are hearing loss, tinnitus and vertigo.
- Other symptoms
  - facial nerve palsy and ataxia.
- occasionally, vertigo and tinnitus are episodic and mimic Ménière's disease
- Physical examination: mass behind the tympanic membrane or growing into the external auditory canal.

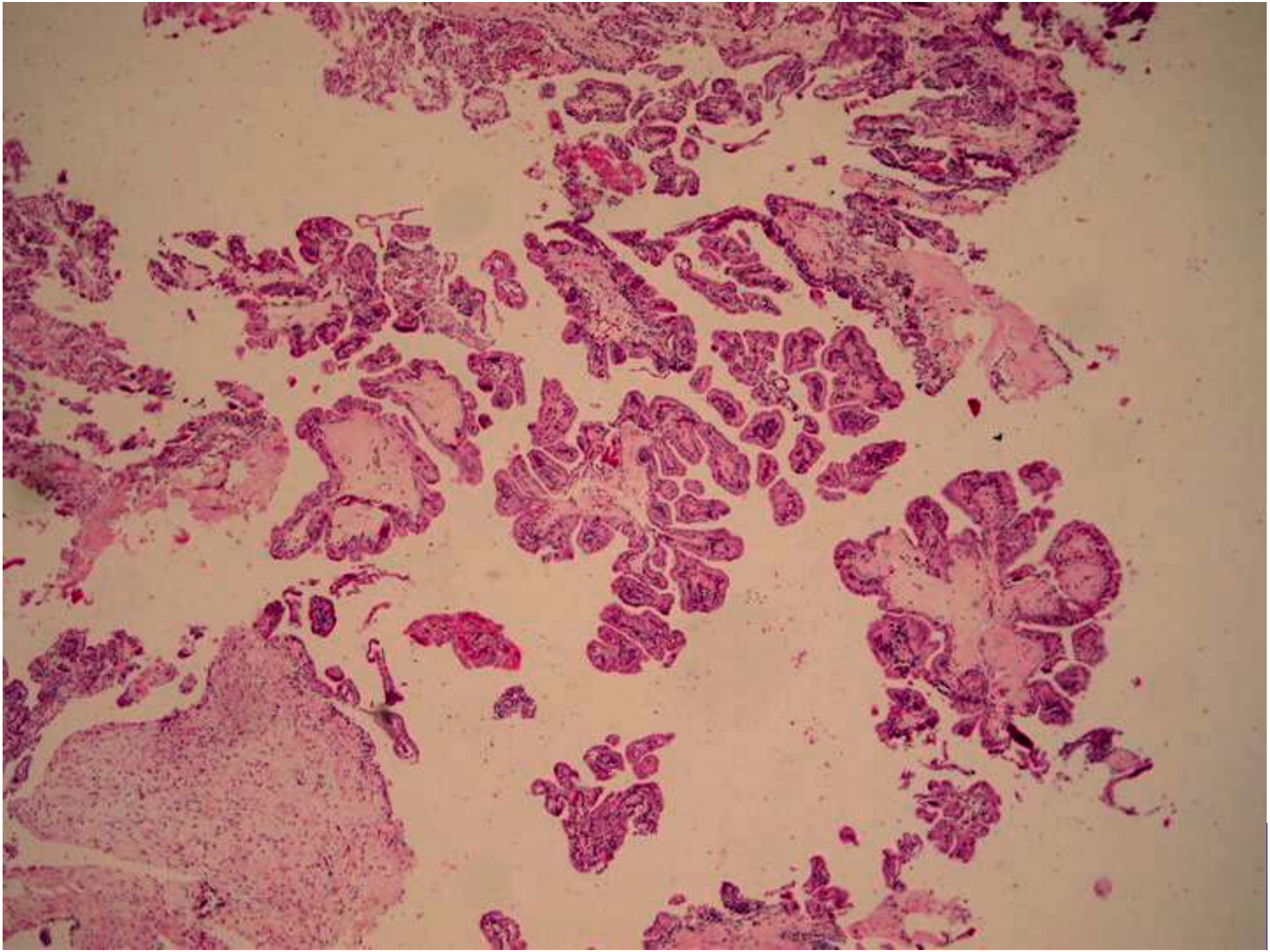
Endolymphatic sac tumor

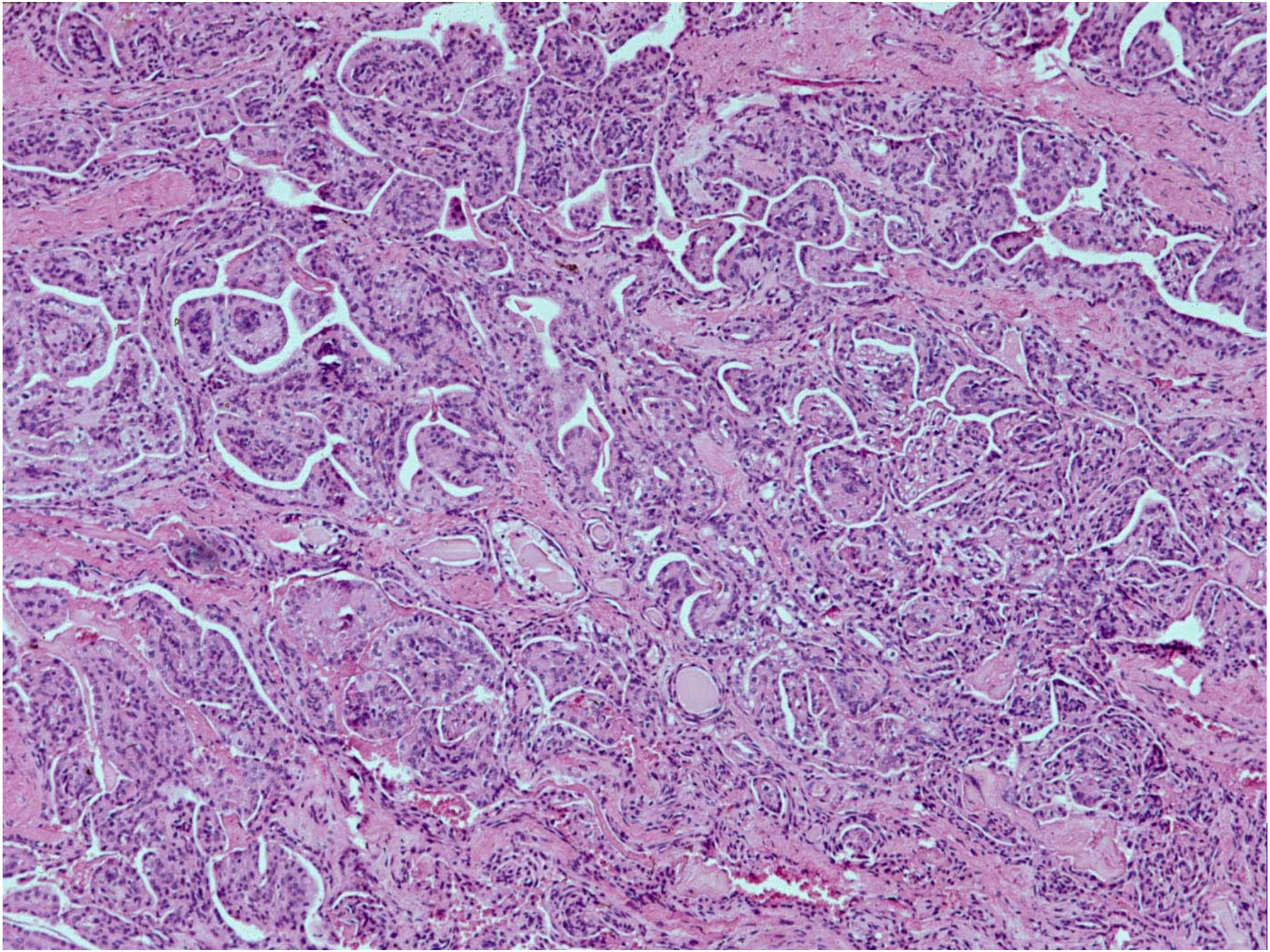
- Imaging studies
  - lytic temporal bone lesion centred in the posterior wall of the petrous portion of the bone.
  - large tumors: may be extension into the posterior cranial fossa with cerebellar involvement or shifting of the fourth ventricle.

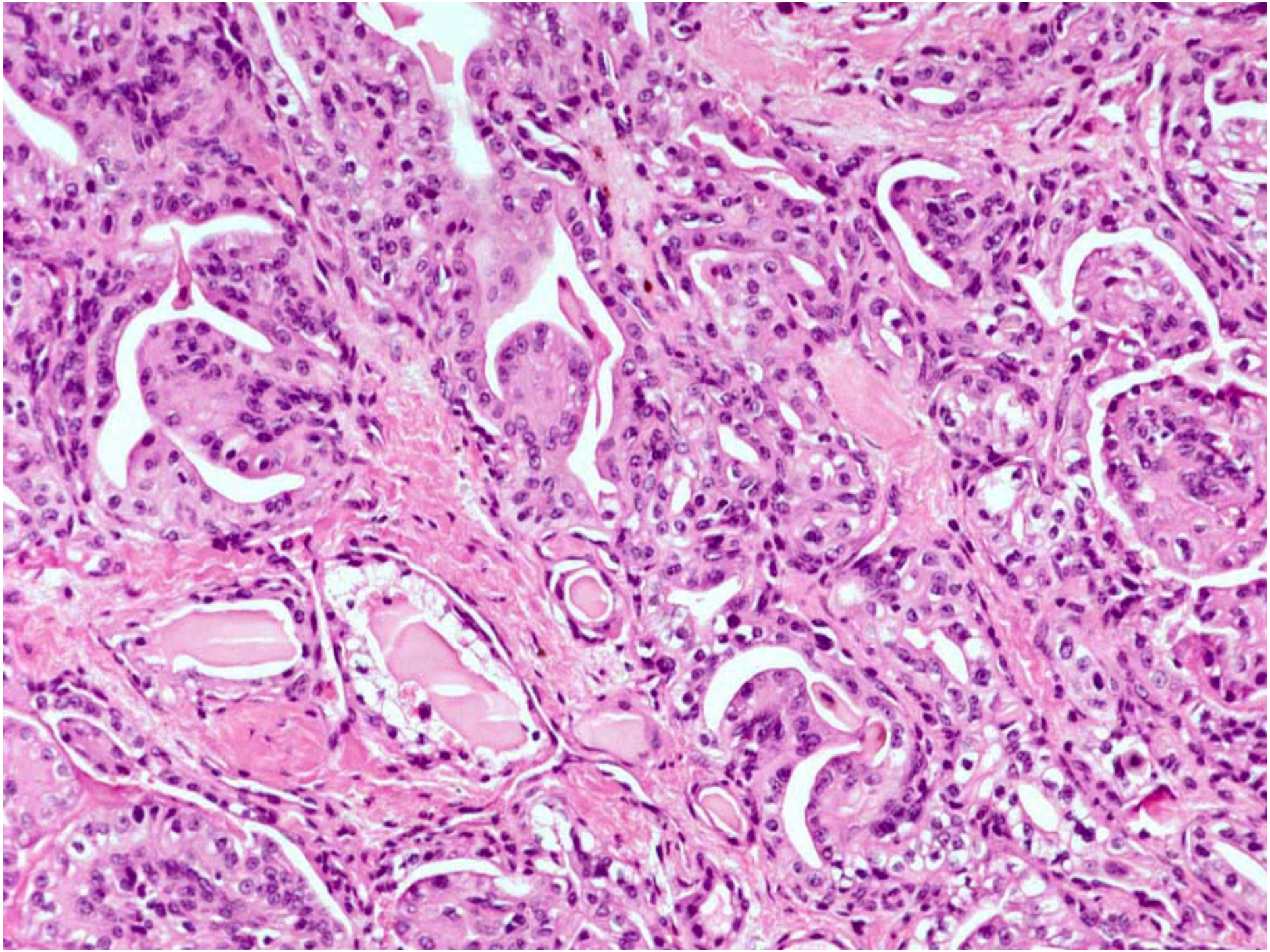
Endolymphatic sac tumor

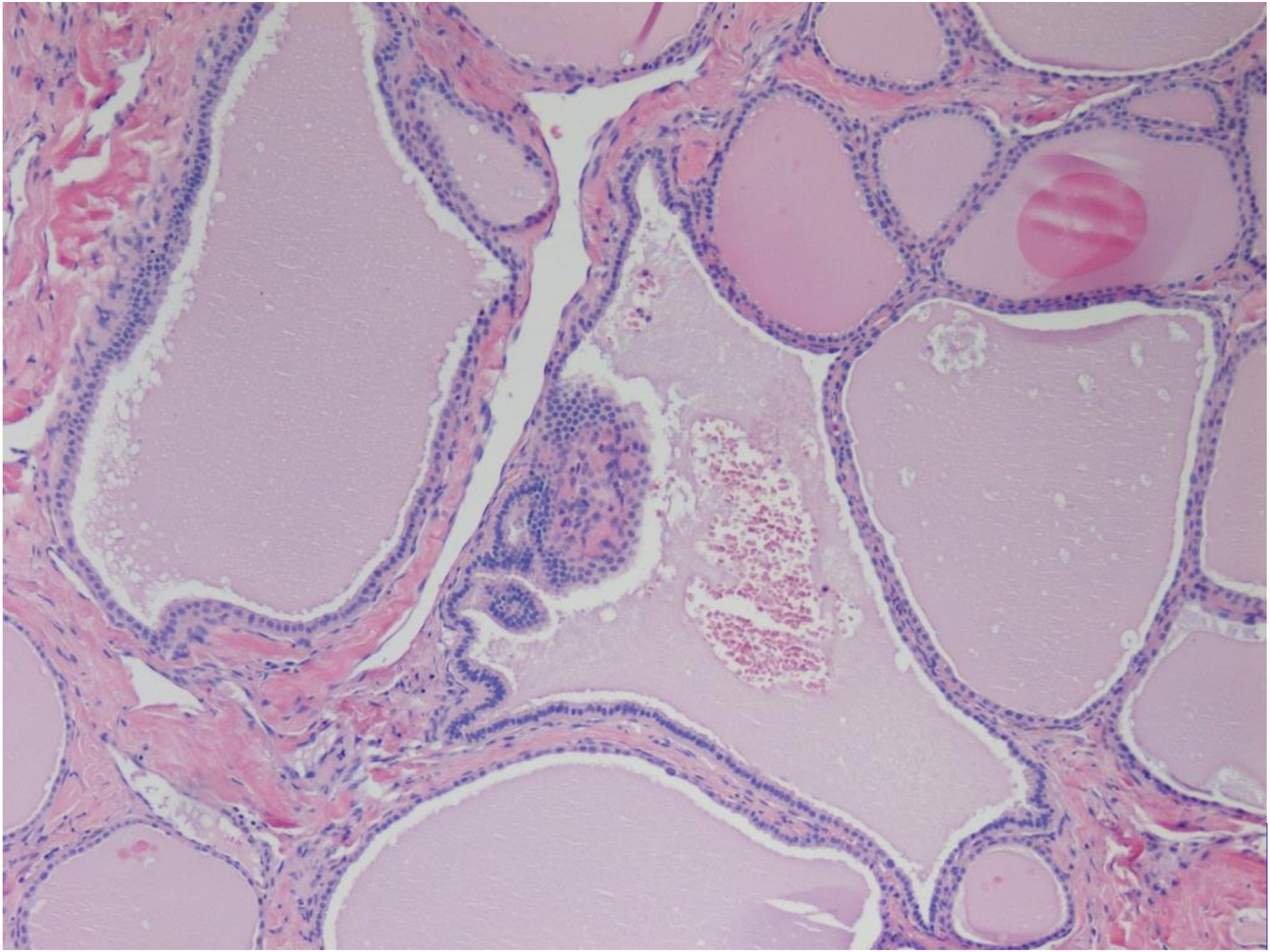
- Microscopic appearance
- Papillary morphology
  - papillae tend to be fairly simple in structure without significant complexity.
  - covering the papillae is a single layer of cuboidal to columnar cells with pale to clear cytoplasm and uniform vesicular nuclei with small nucleoli
- Follicle-like structures
  - containing material resembling colloid
  - having an appearance like thyroid tissue
- Areas of fibrosis with hemosiderin-laden macrophages may present
- Cytologic features of malignancy are absent and tumoral necrosis is not seen.

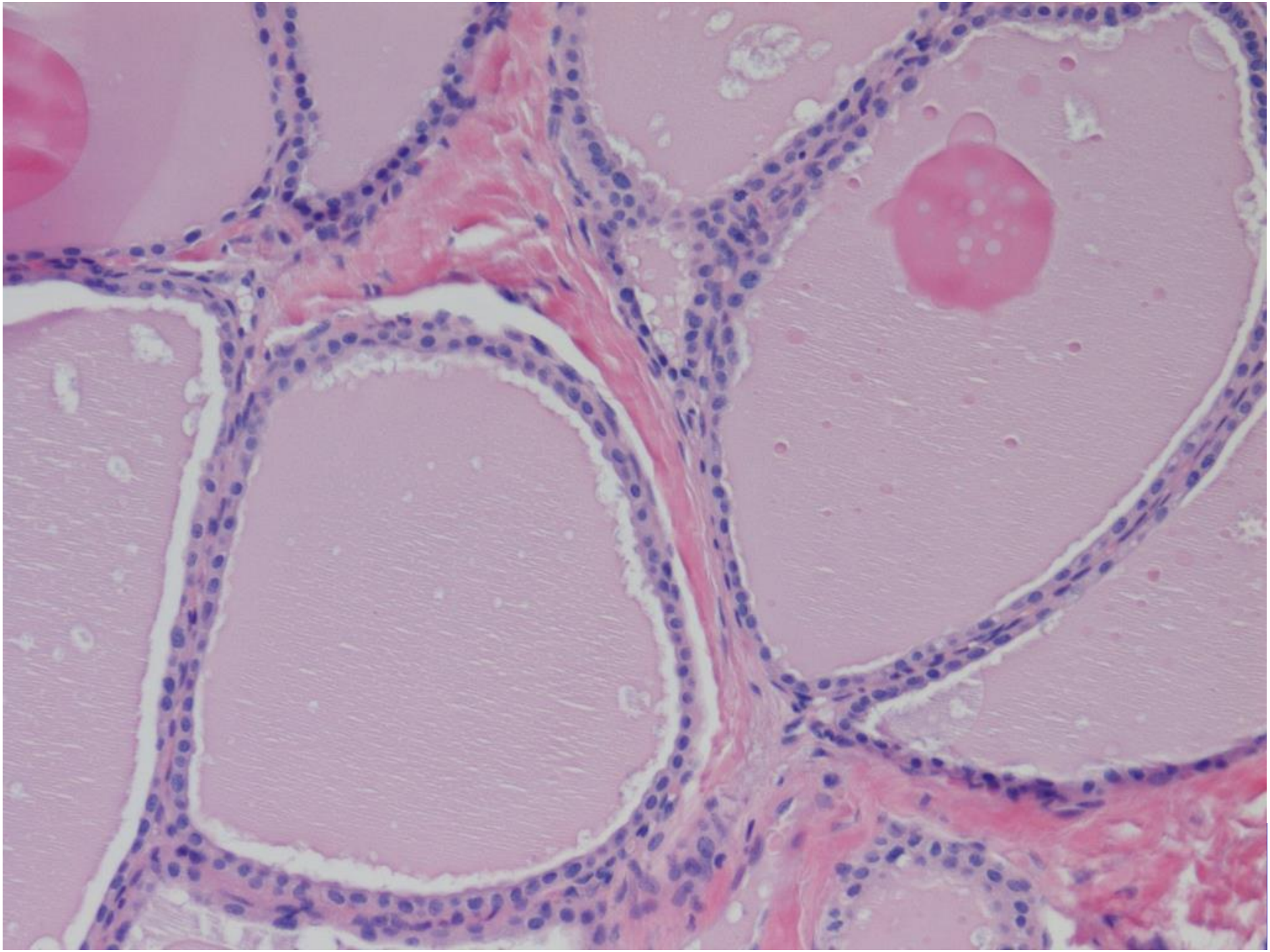


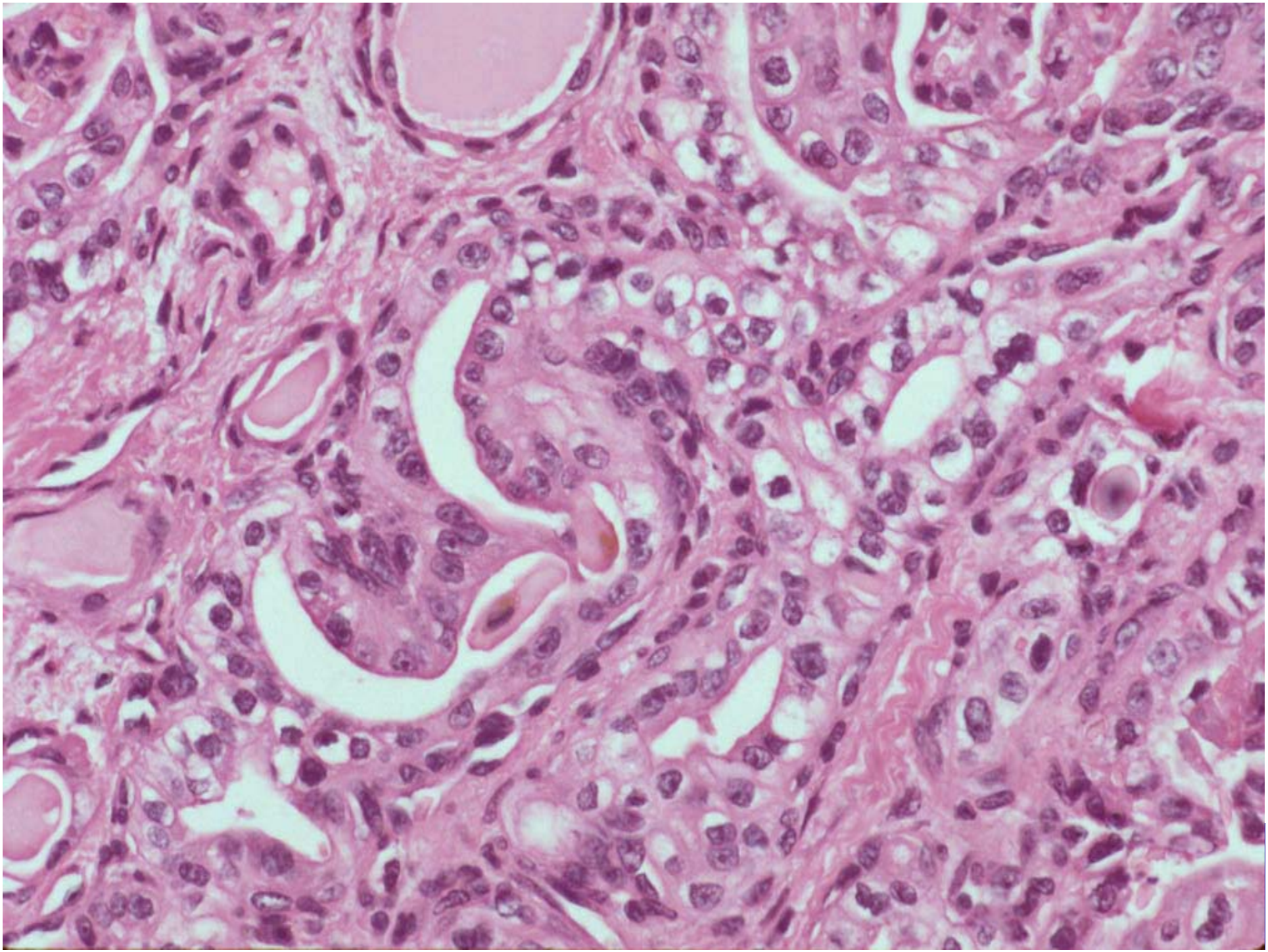


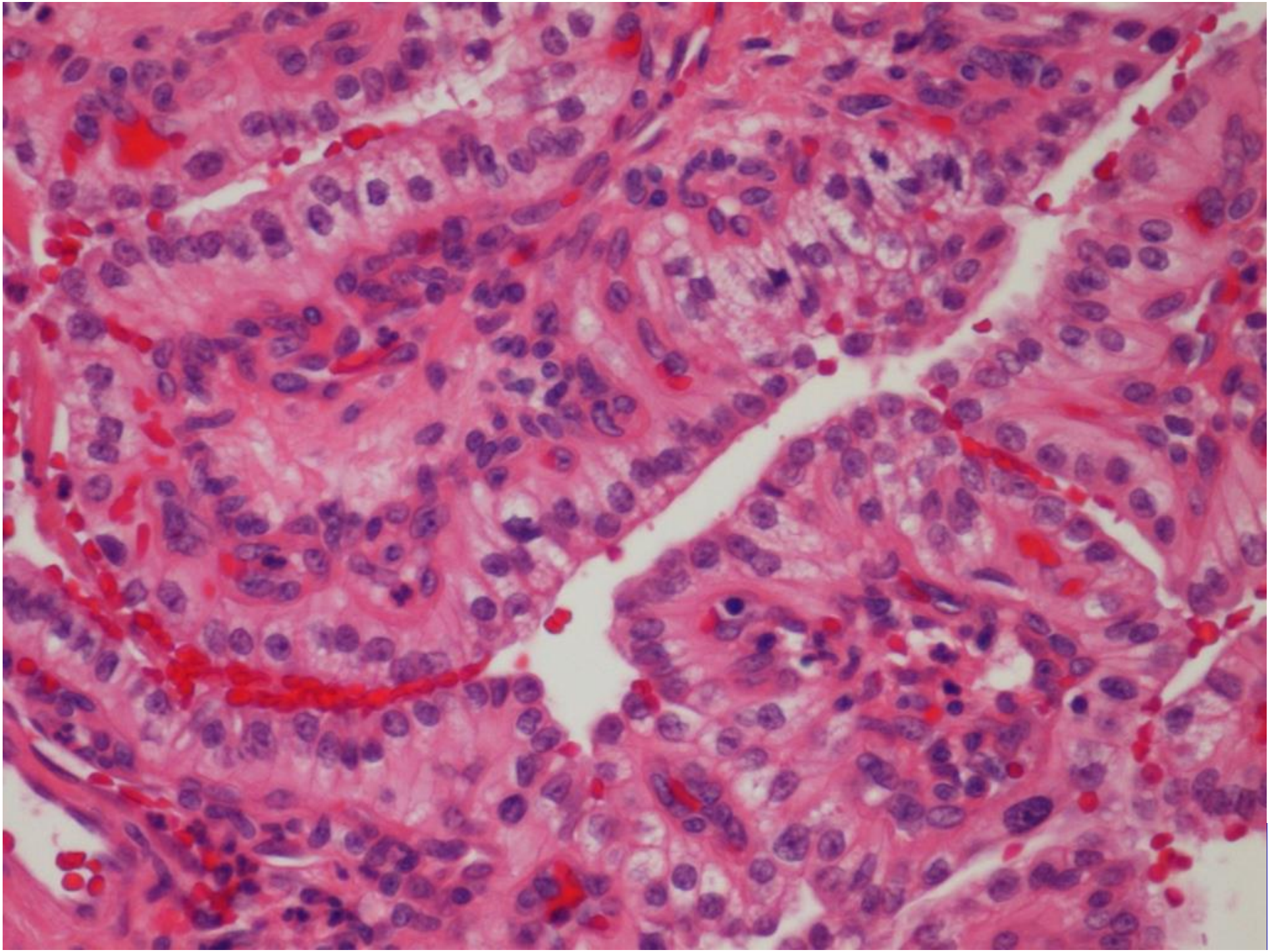


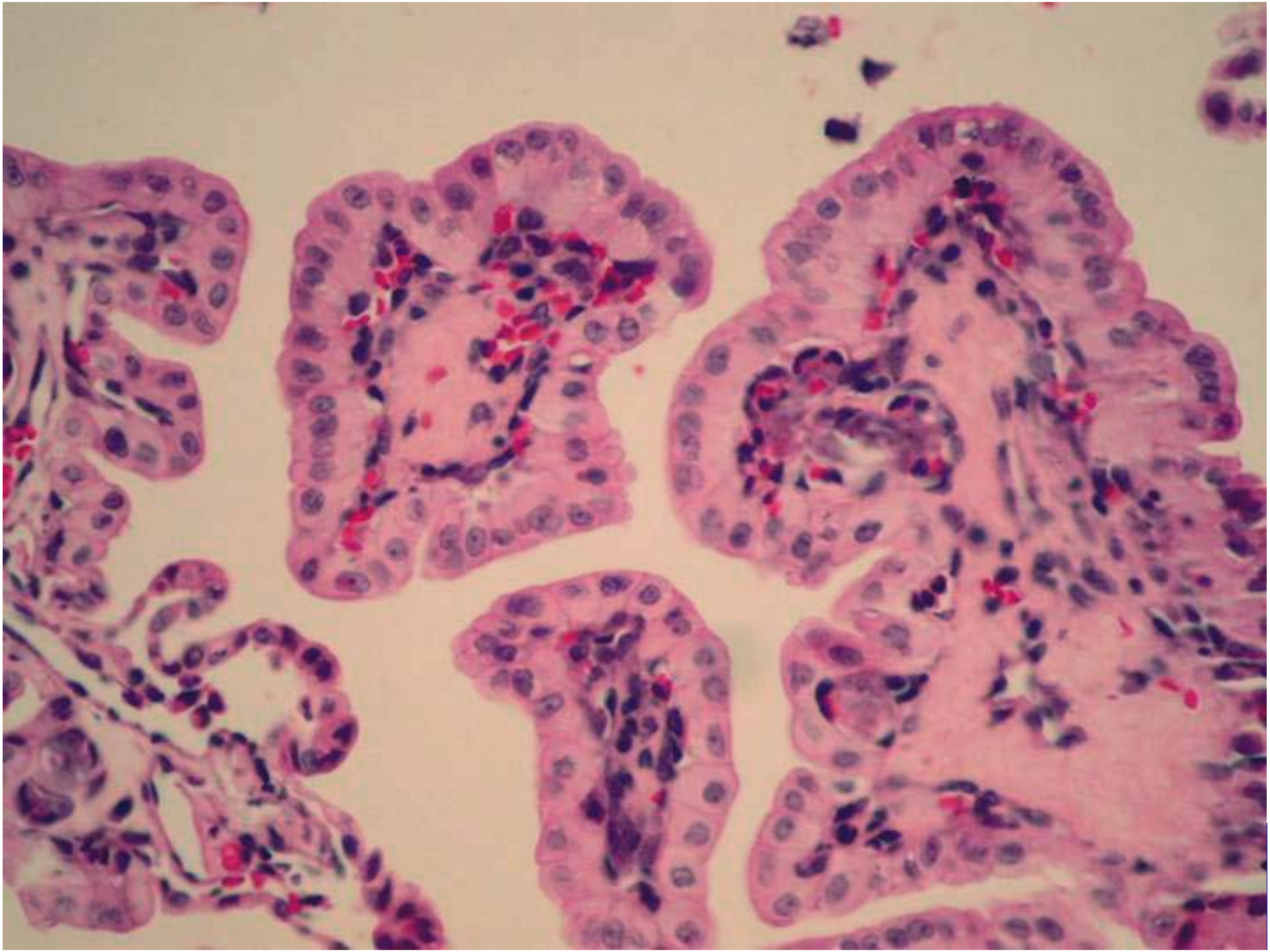


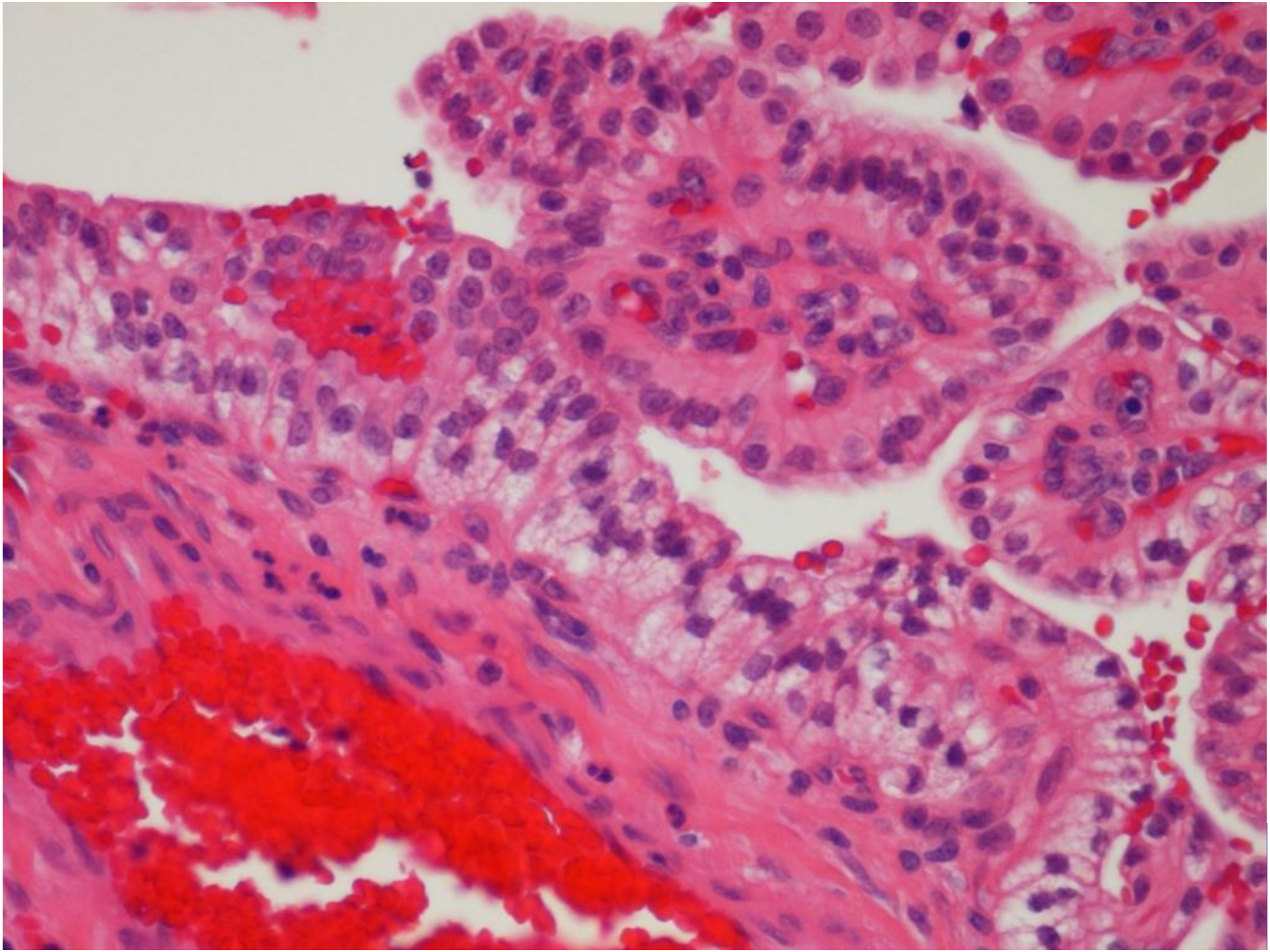












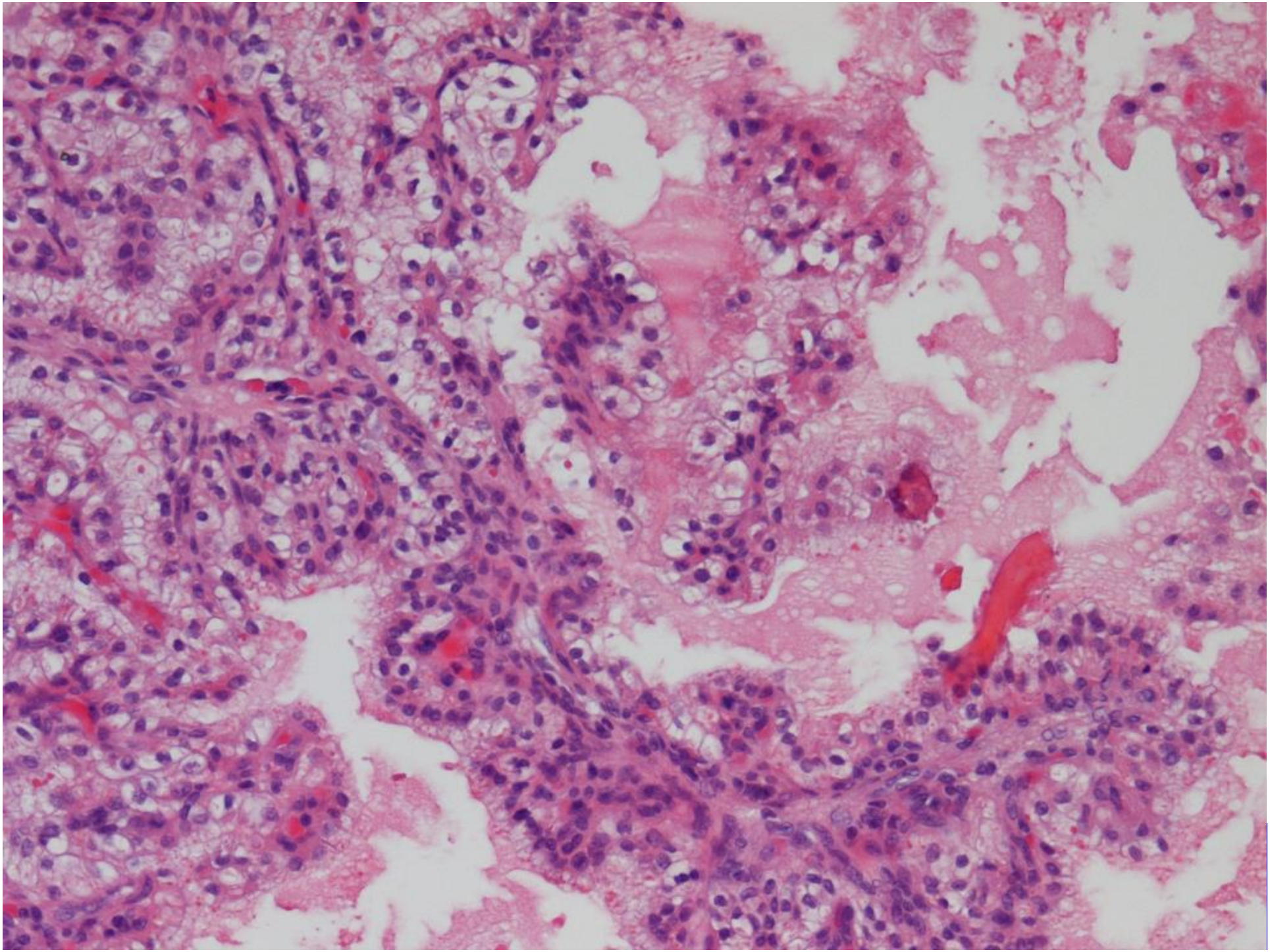
Endolymphatic sac tumor

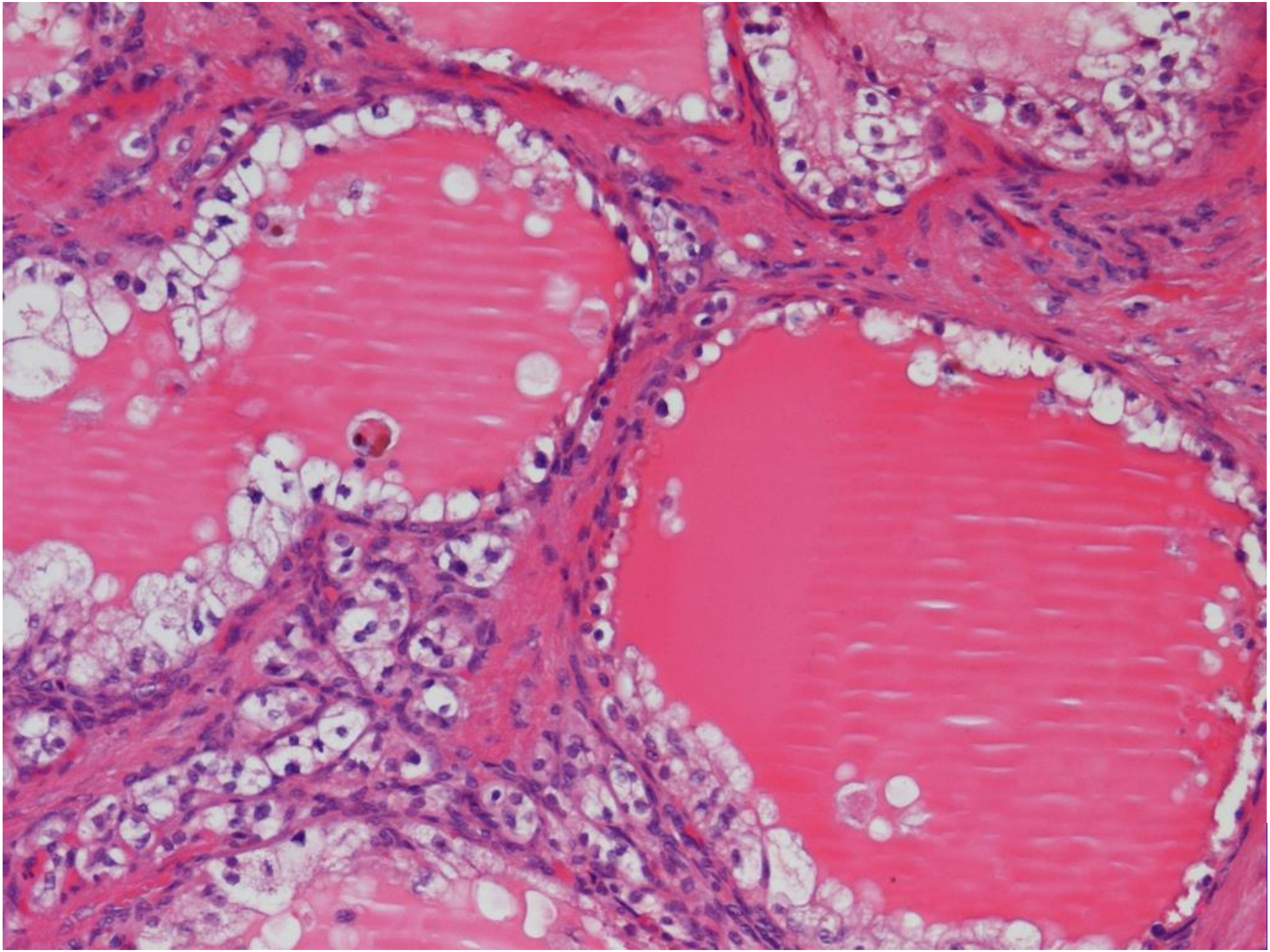
- Immunohistochemical stains:
  - positive for cytokeratin
  - weak positivity for S100, GFAP, EMA and synaptophysin
  - TTF-1 and thyroglobulin stains are negative

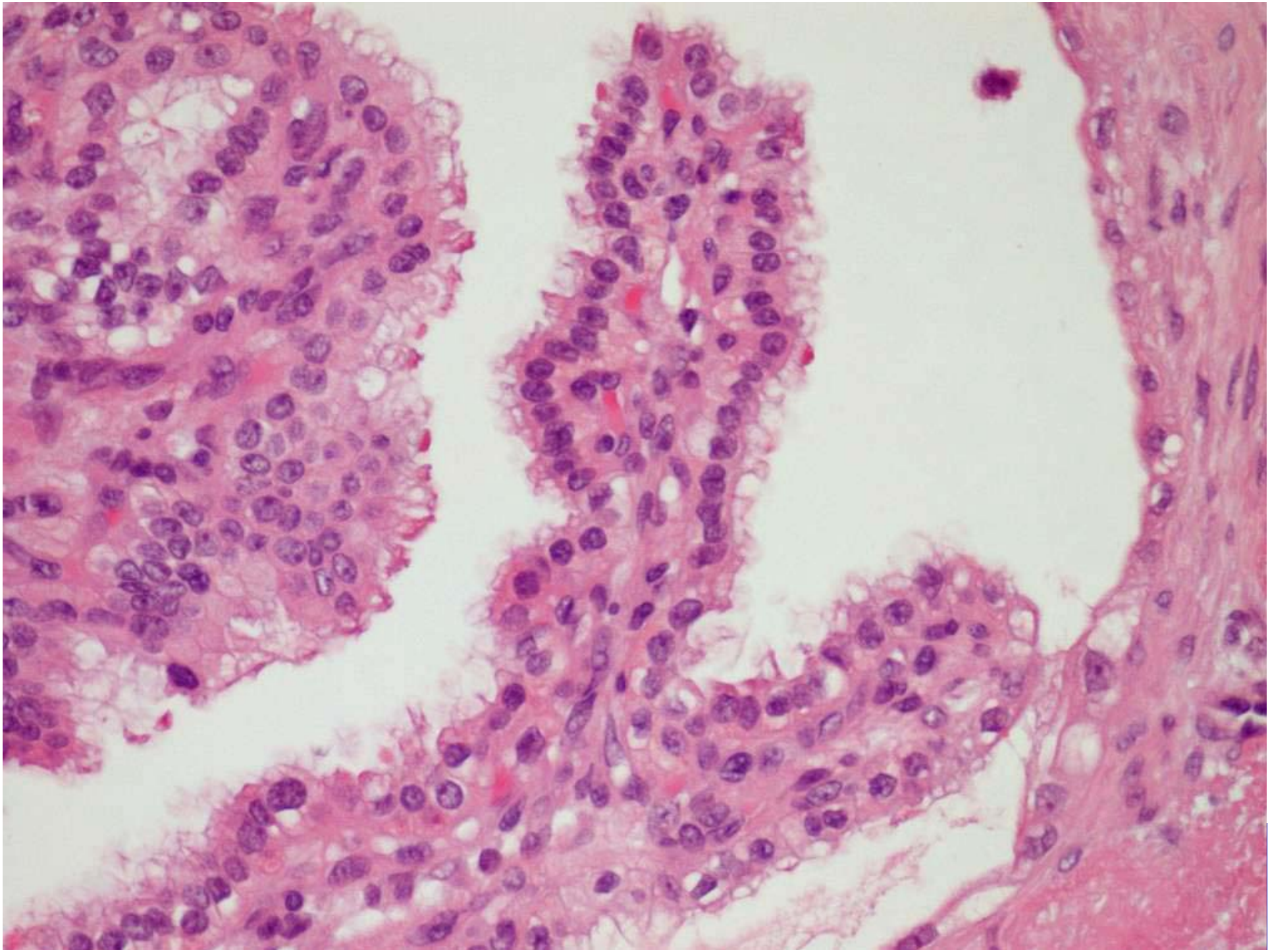
Endolymphatic sac tumor

Relationship to von Hippel-Lindau syndrome

- Estimated that individuals with von Hippel-Lindau syndrome (VHL) have about a 10% likelihood of developing ELST.
- ELST in VHL may be bilateral
- In one patient with VHL, a small clinically silent tumor was found involving the ELS at autopsy in a patient with a large destructive ELST on the contralateral side.
- The morphology of ELST is very similar to papillary cystadenoma of the epididymis, a tumor that is common in VHL.







Endolymphatic sac tumor Differential diagnosis

- Middle ear adenoma
  - MEA is confined to the middle ear and does not erode bone
  - No or minimal papillary architecture
  - Immunohistochemical evidence of neuroendocrine differentiation

- Metastatic adenocarcinoma
  - most common carcinomas to metastasize to temporal bone: breast, lung, kidney, stomach and larynx.
  - Melanoma also metastasizes not infrequently to temporal bone.
  - Most patients have known tumor with other evidence of metastatic disease
  - Renal cell carcinoma (VHL)
    - no consistently useful immunohistochemical markers to aid in this differential
  - Papillary carcinoma of thyroid
    - TTF1 or thyroglobulin antibodies.

Endolymphatic sac tumor

- Treatment for ELST is surgical and typically involves radical resection of mastoid and temporal bone and may include sacrifice of cranial nerves.
  - This approach leads to good results. Inadequate resection leads to recurrence and subsequent reoperation may prove very difficult.
- The role of radiotherapy is unclear, but it is typically used for tumors where complete excision is not possible.

Jugulotympanic paraganglioma

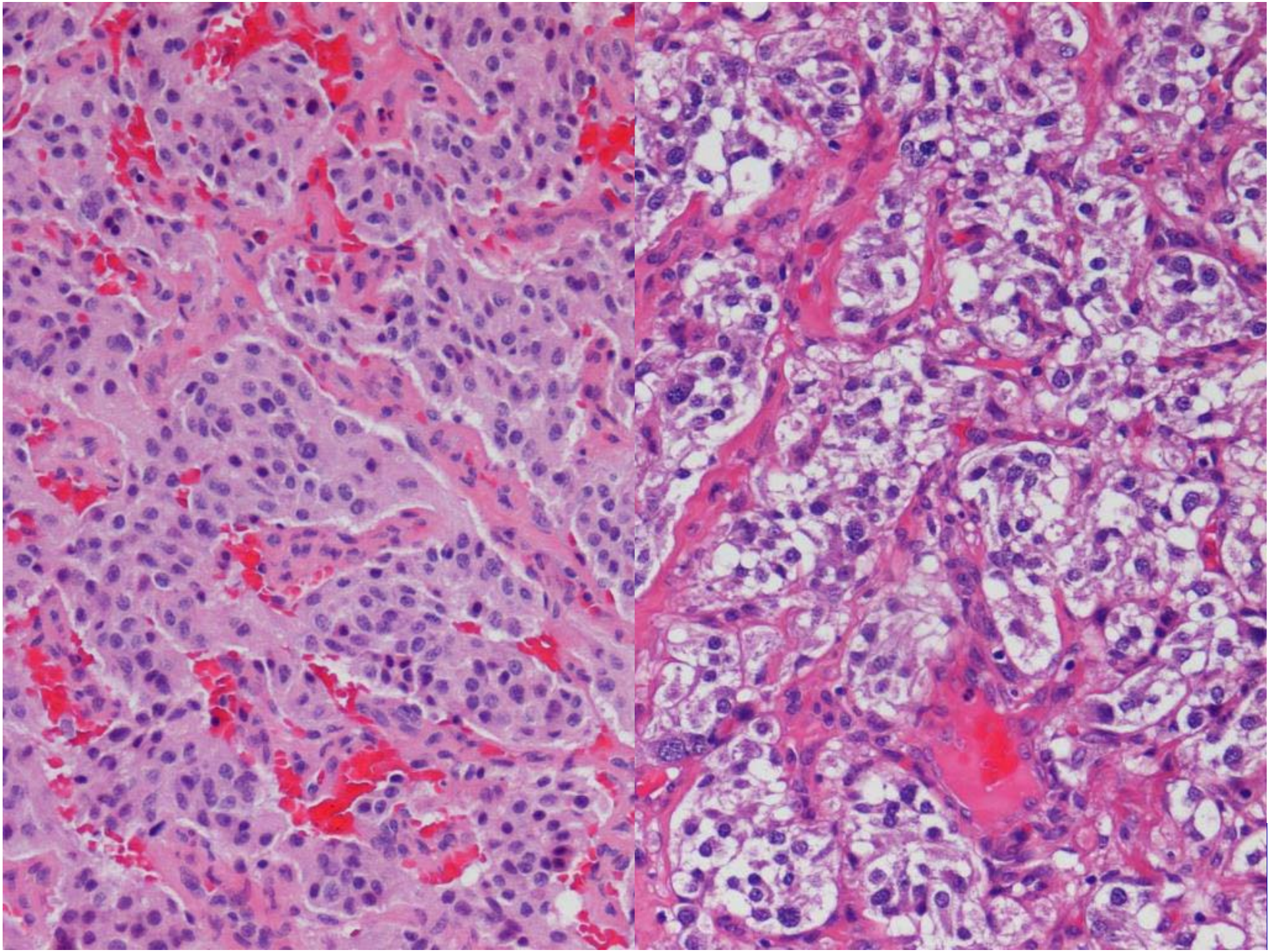
- Paragangliomas involving the middle ear and temporal bone most common neoplasms of this region
- second most common extraadrenal paraganglioma, after carotid body tumor
- Classification
  - glomus typanicum: arise within the middle ear from the paraganglia that follow the auricular branch of the vagus nerve or the tympanic branch of glossopharyngeal nerve
  - glomus jugulare: arise within the jugular bulb

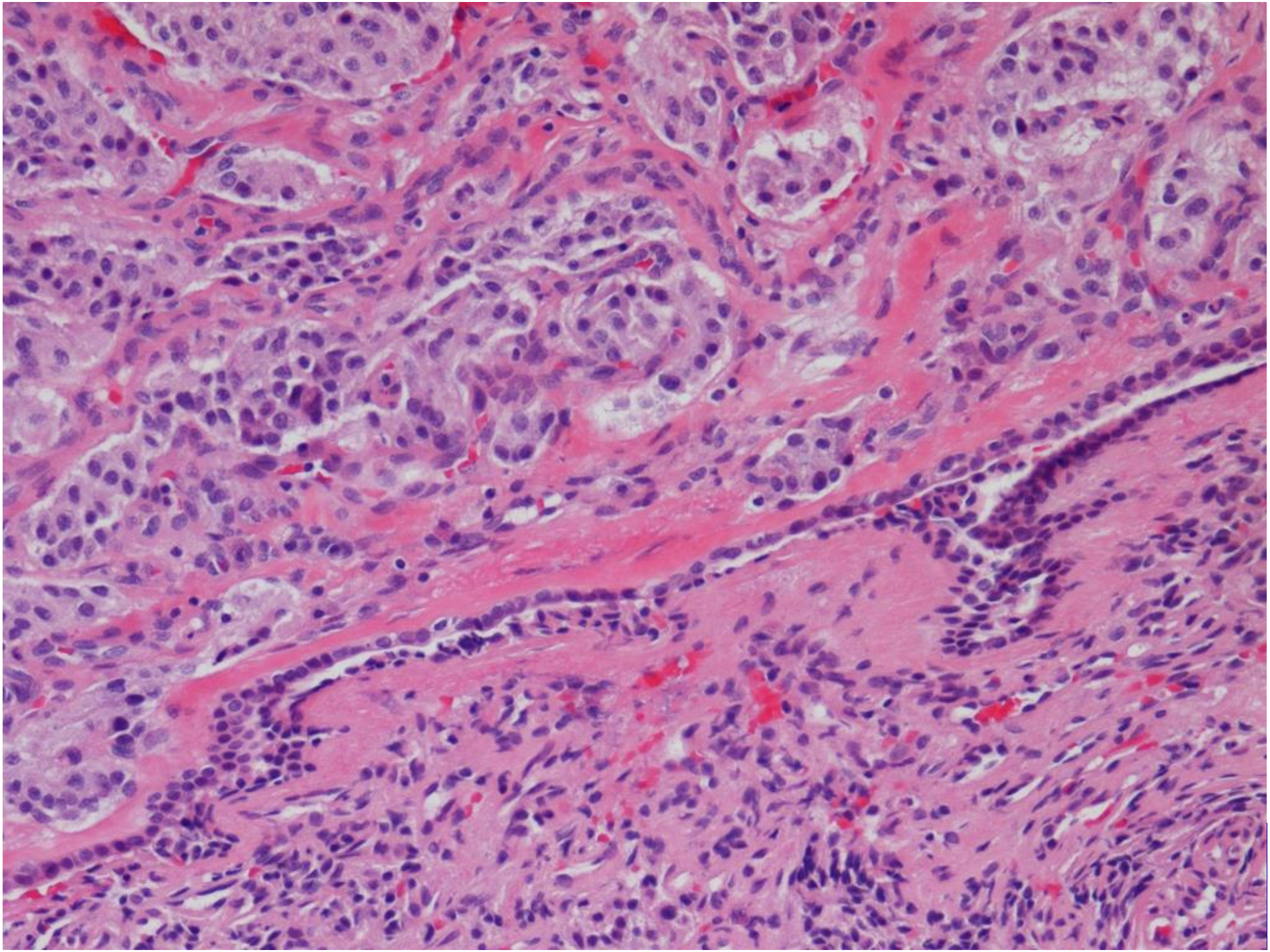
Jugulotympanic paraganglioma

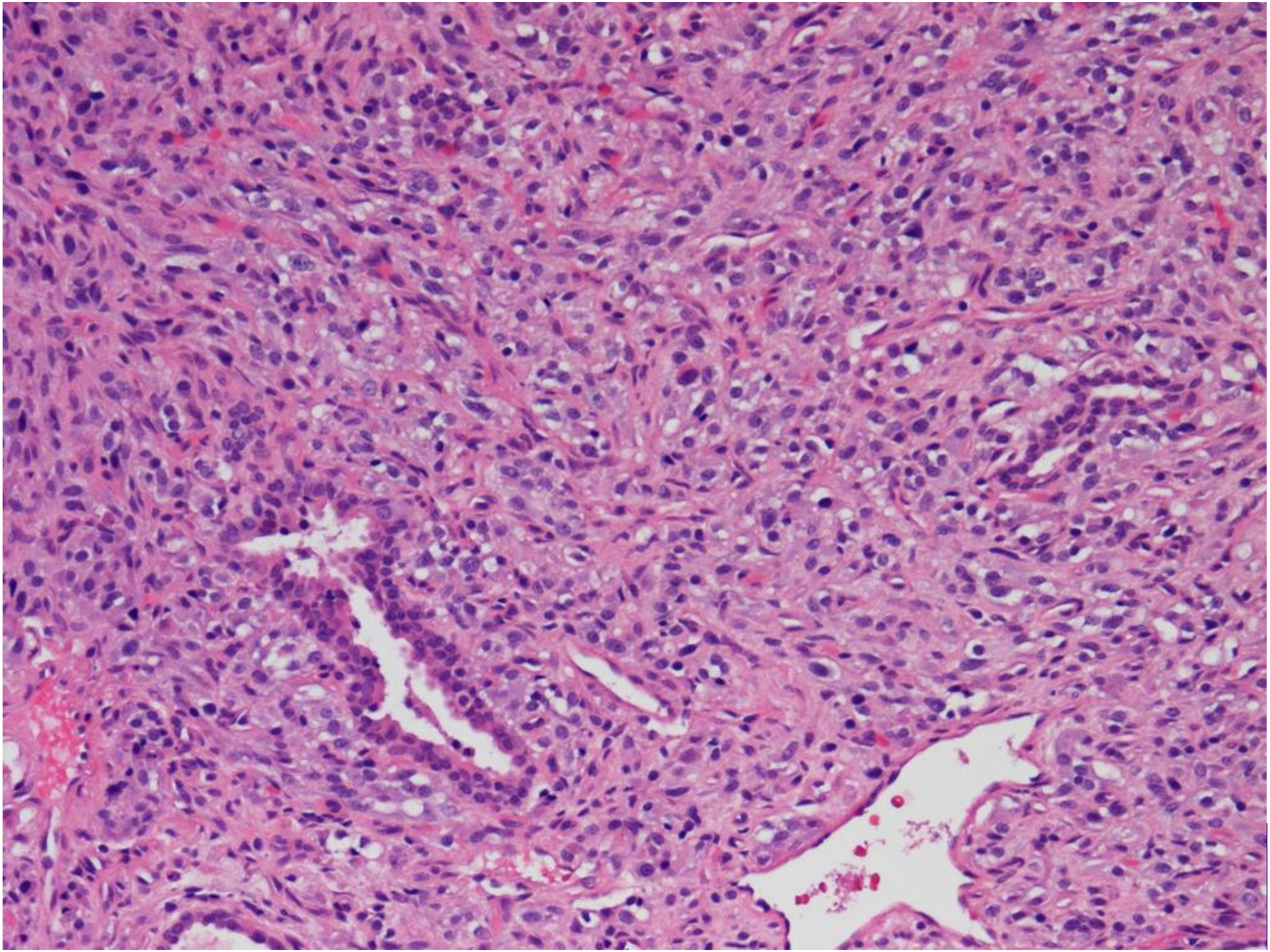
- Adults
- male:female ratio of approximately 1:3
- Symptoms based on the site of origin:
  - Glomus tympanicum tumors typically produce symptoms related to ear function early in their course such as hearing loss, tinnitus (frequently pulsatile), or vertigo
  - Glomus jugulare tumors reach considerable size before symptoms develop, and then often have cranial nerve palsies in addition to the symptoms described above
- Reddish mass behind the tympanic membrane or protruding into the external auditory canal.
- Symptoms related to functioning tumor are exceptionally uncommon, probably in the order of 1%.

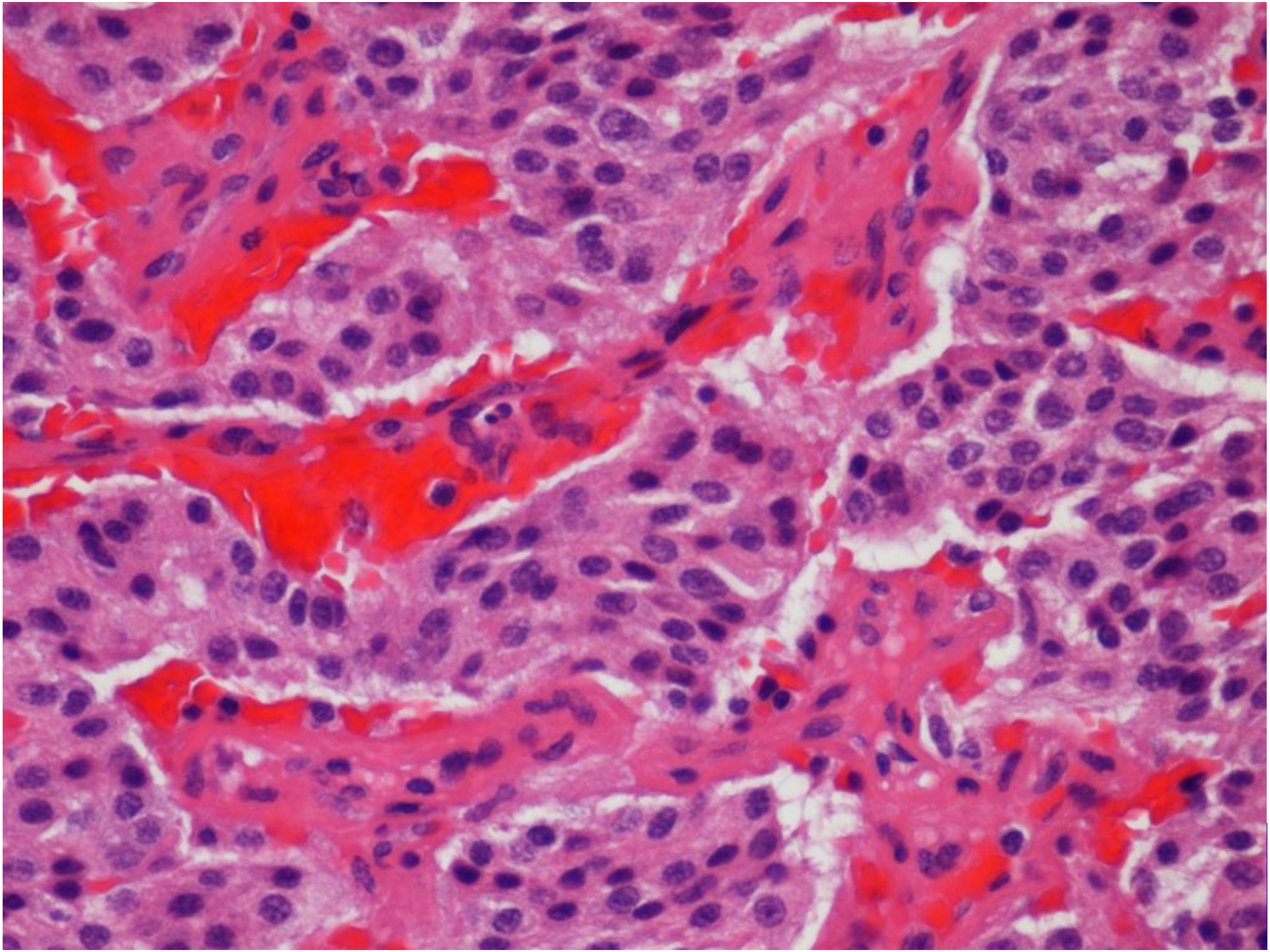
Jugulotympanic paraganglioma

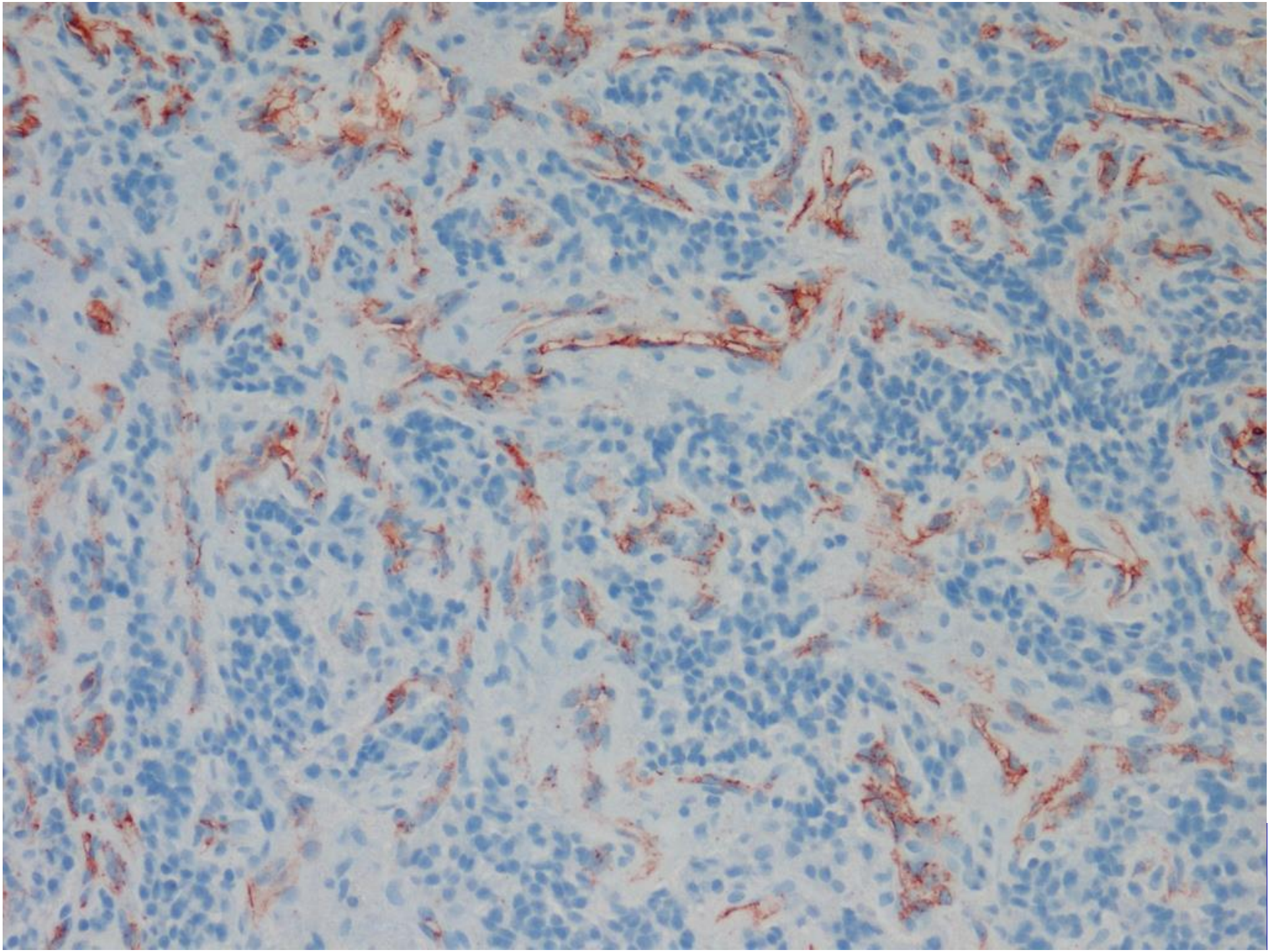
- Diagnosis of JTP is based on clinical examination together with imaging studies
- CT is very useful to determine the degree of bony destruction
- MRI with gadolinium contrast is very useful and will show a characteristic salt and pepper appearance on T1-weighted images
- MRI is useful for demonstrating multifocality.

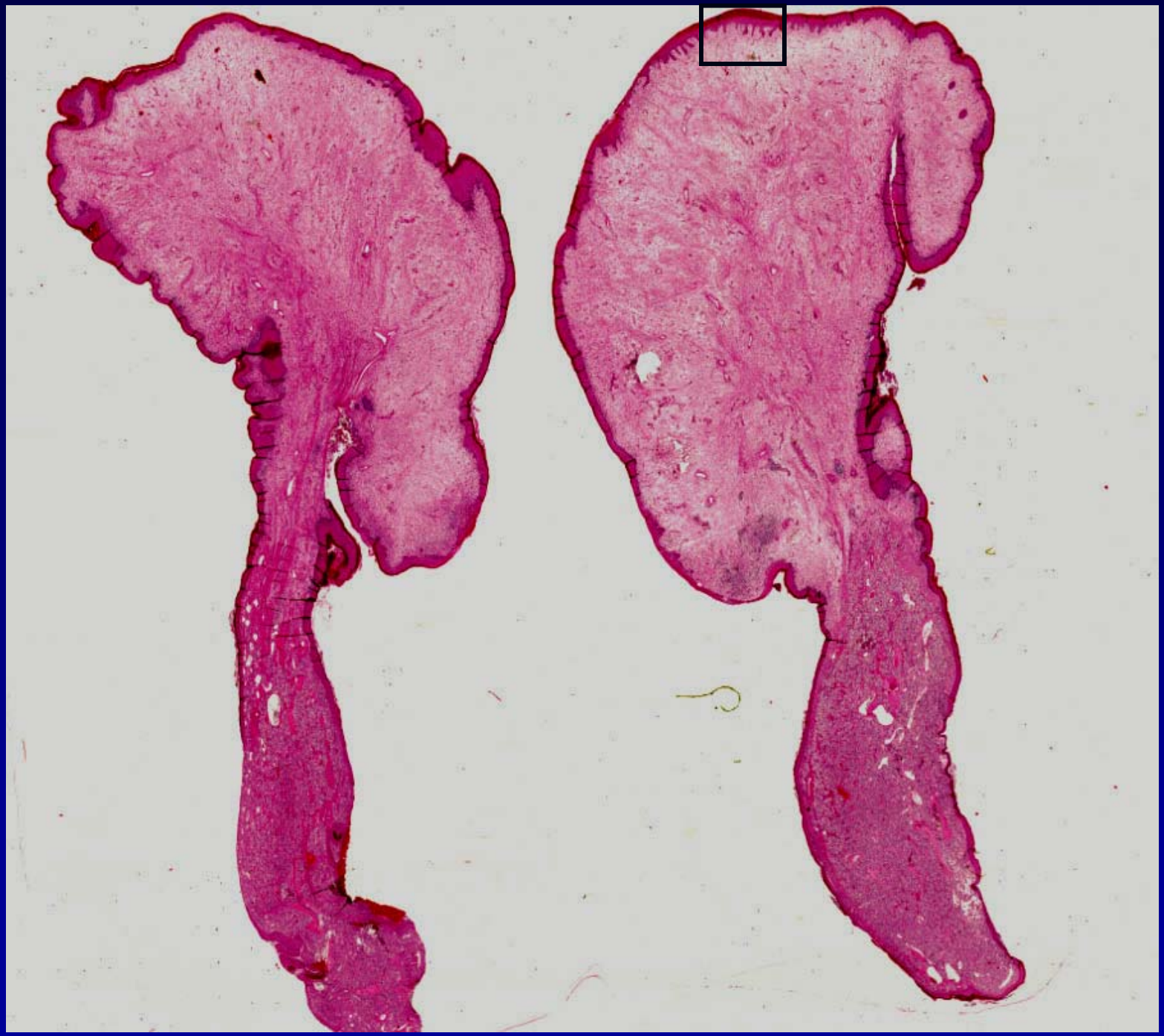


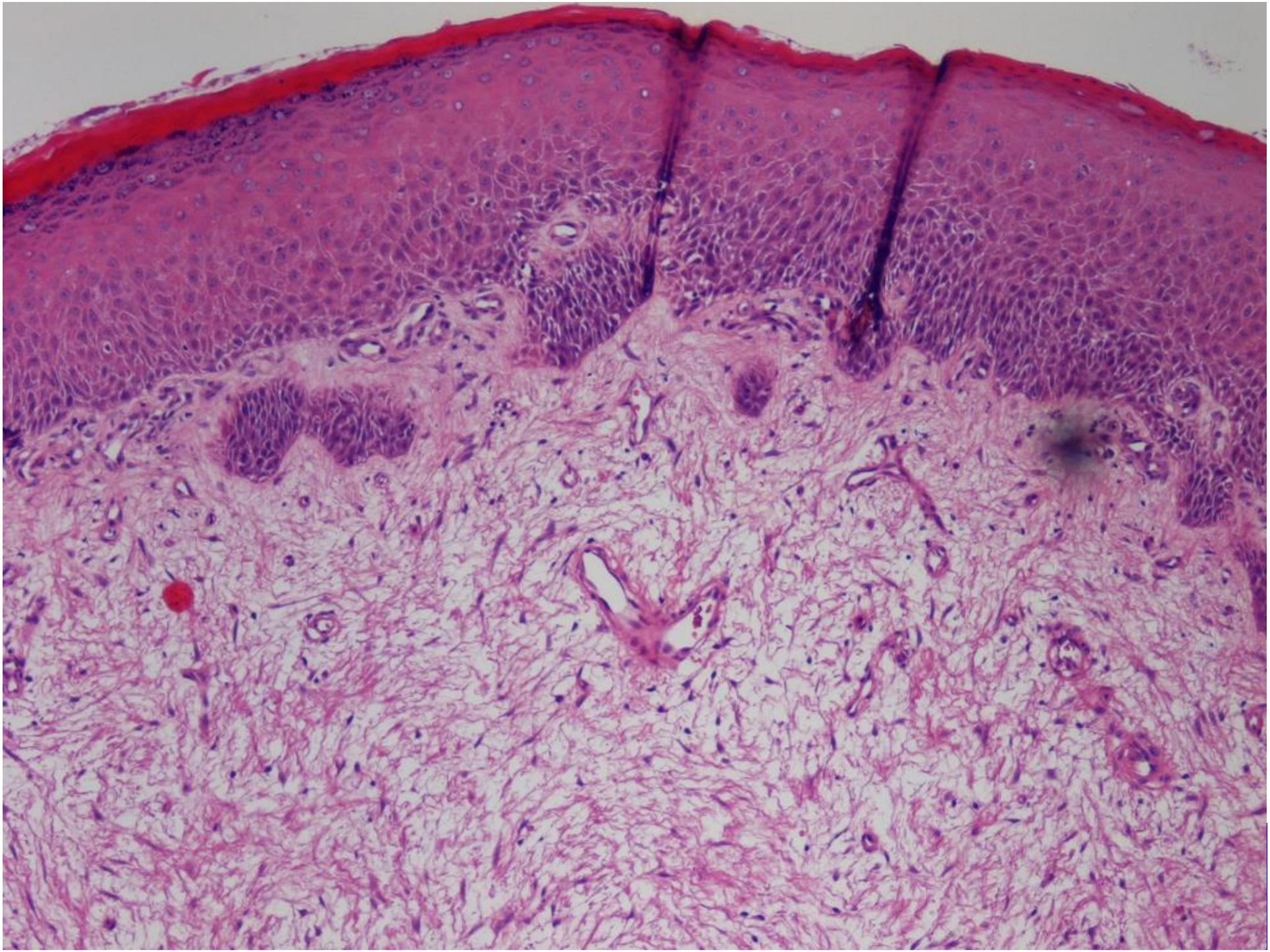


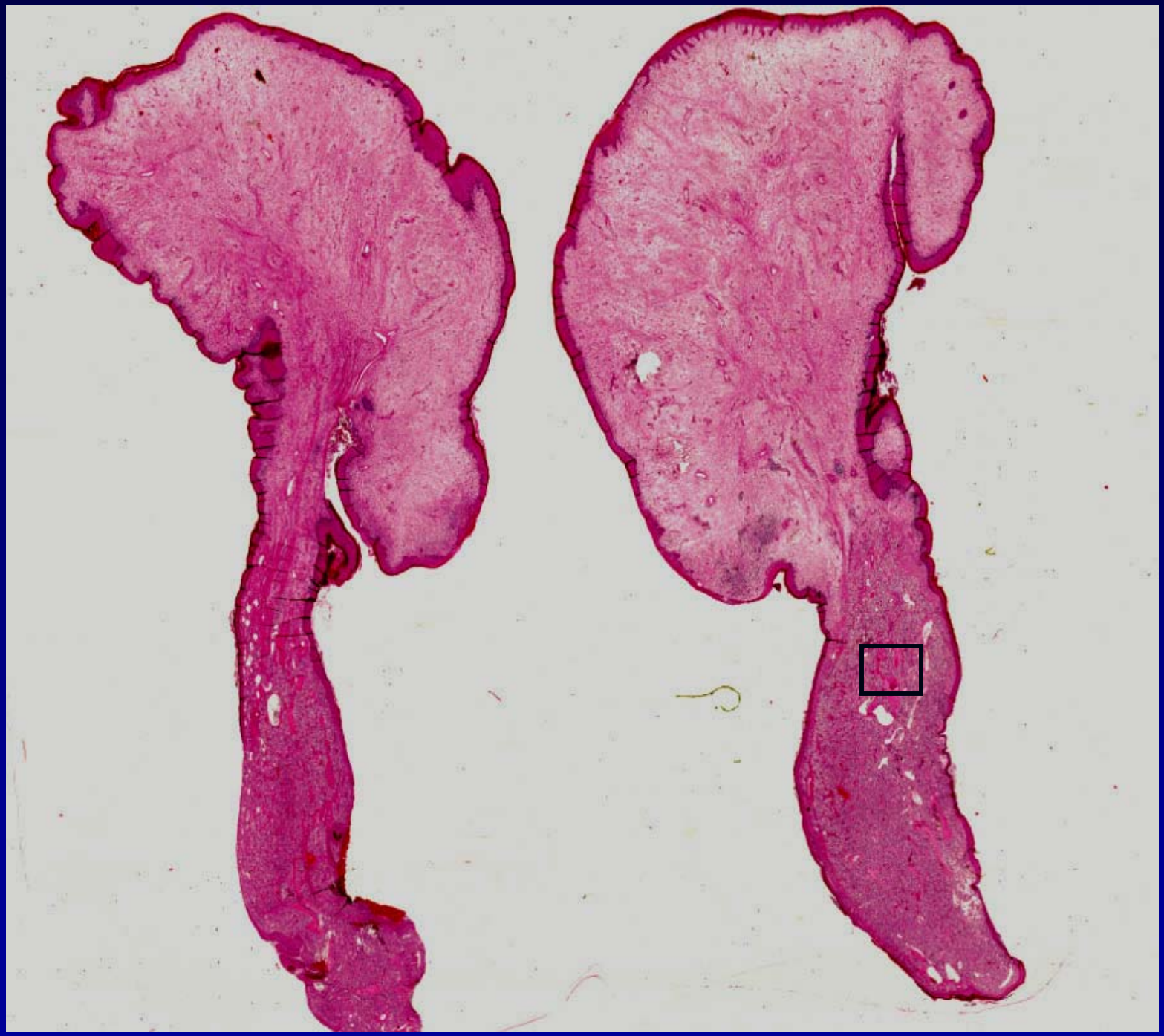


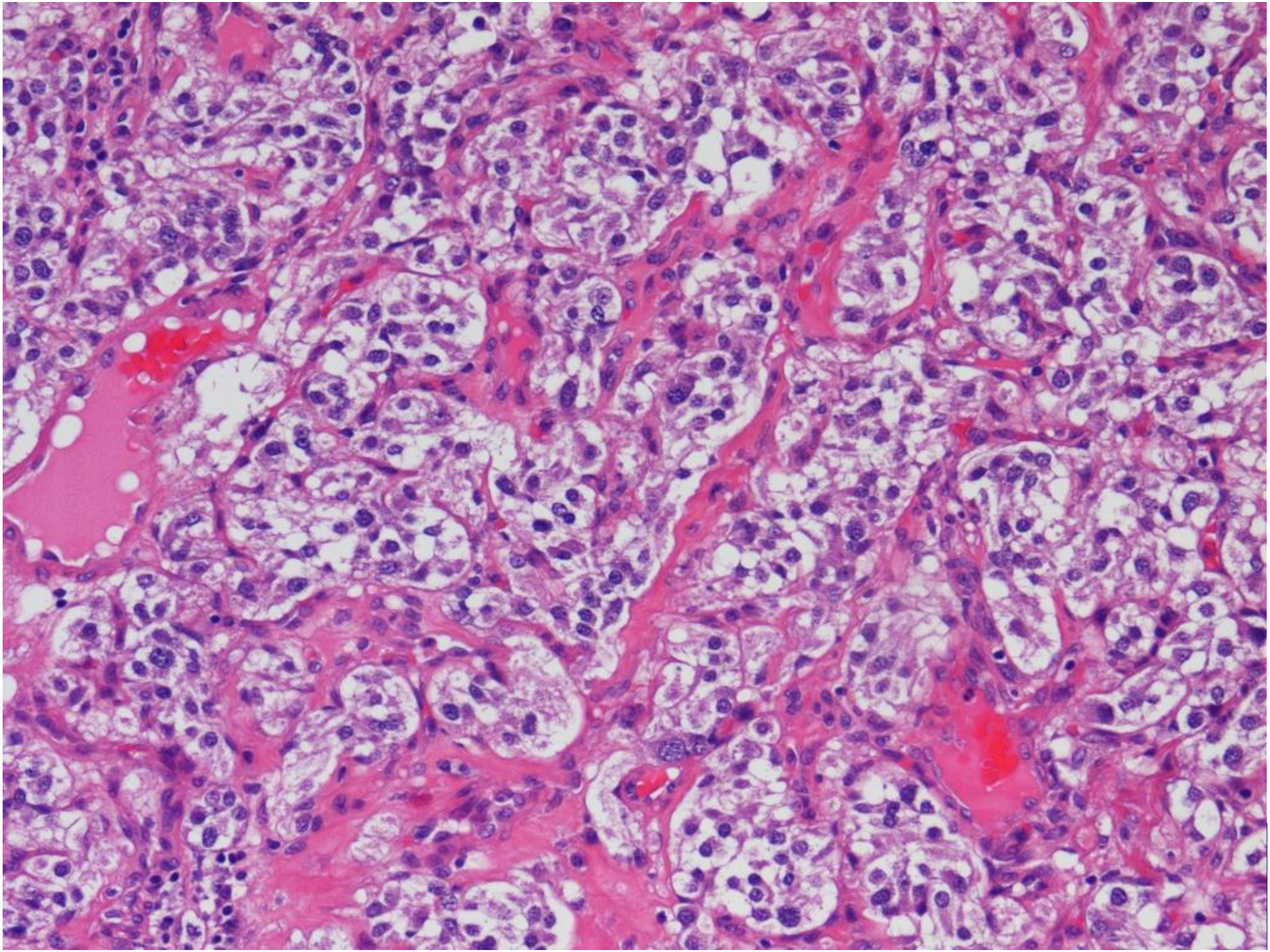


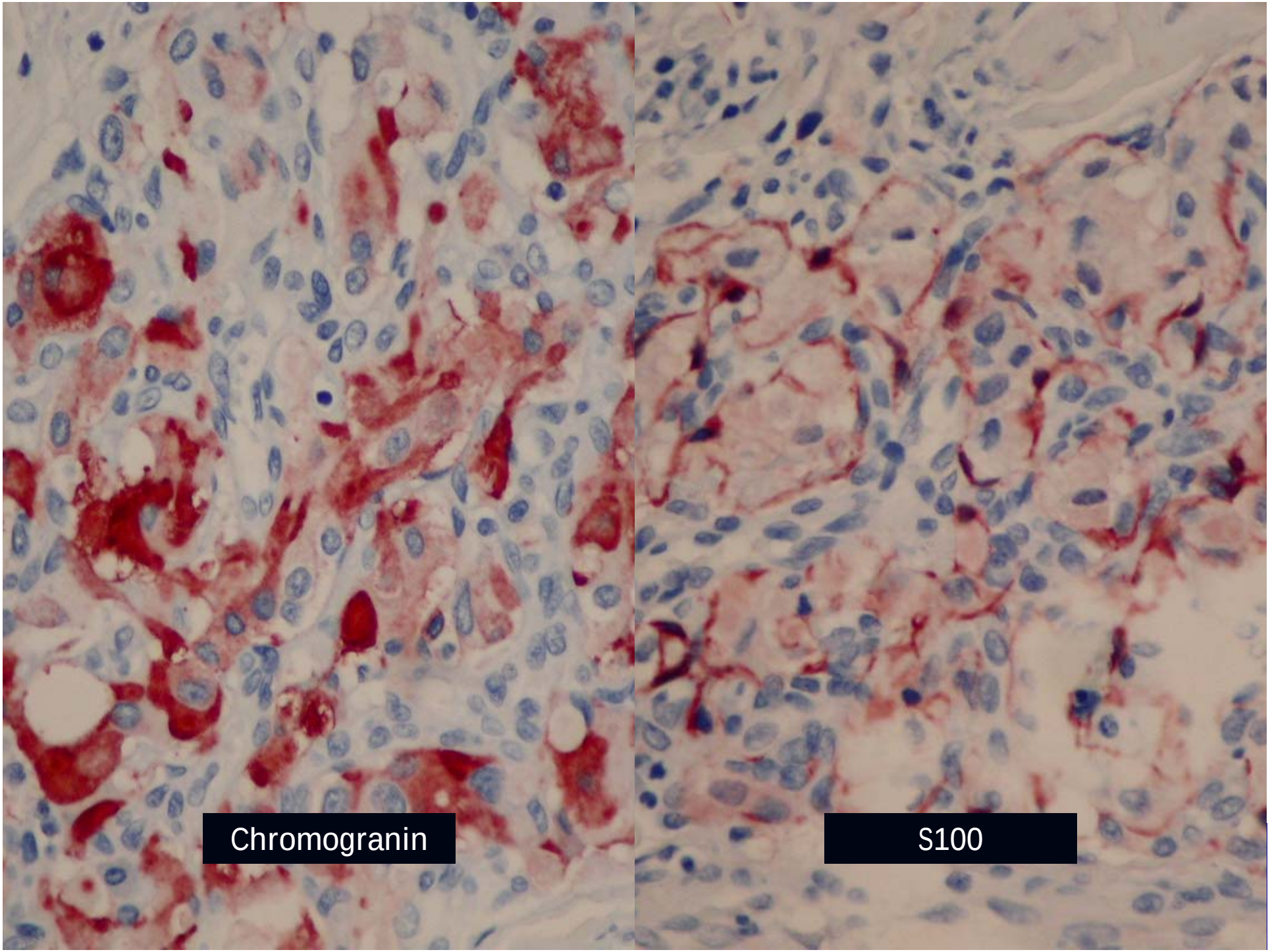











Chromogranin
S100

Jugulotympanic paraganglioma Differential diagnosis

- MEA/C, ELST, meningioma, and metastatic carcinoma
- most of the neoplasms in the differential diagnosis lack the vascularity that characterizes JTP on imaging
- In addition, with the exception of MEA, which typically is an avascular mass on imaging, all of these tumors in the differential diagnosis lack neuroendocrine differentiation
- The finding of chromogranin and synaptophysin positivity thus rules them out with the exception of MEA
  - S100 staining with a sustentacular cell distribution is very helpful in the differential diagnosis

Jugulotympanic paraganglioma

Treatment

- Surgical
  - approach varies depending on the site and extent of disease.
  - recurrence rates are high (50%) for large tumors

Prognosis

- Metastases, most often to lung and bone, less often to liver and regional lymph nodes, are said to occur in less than 4% of cases
- Death, in up to 15%, is related to local extension into cranial vault or metastatic disease.

Ear and Temporal Bone Pathology

- Ceruminous gland tumors can be classified into one of the four types indicated in this presentation and prognosis and treatment determined
- Group of middle ear neoplasms that are interesting pathologically and require additional study