Recent Developments in Salivary Gland Pathology

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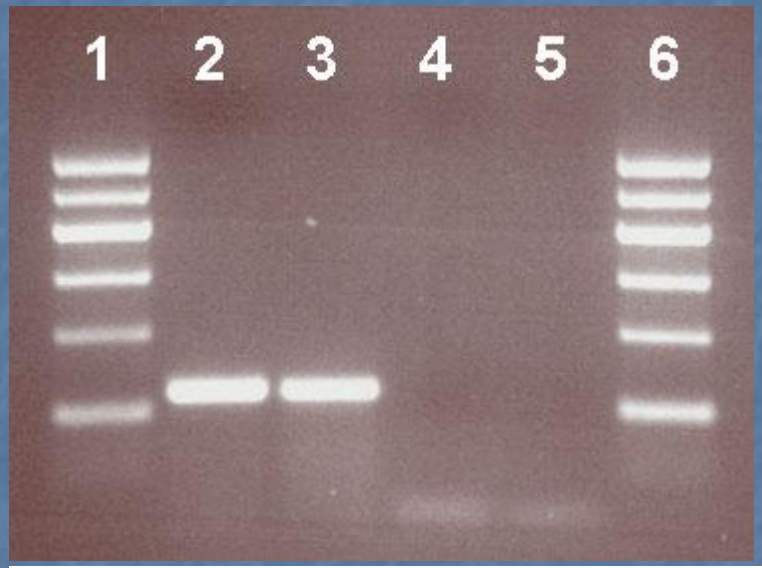
- Update on molecular diagnostics of salivary gland tumors
- Newly recognized entities
- Known tumor entities with new findings

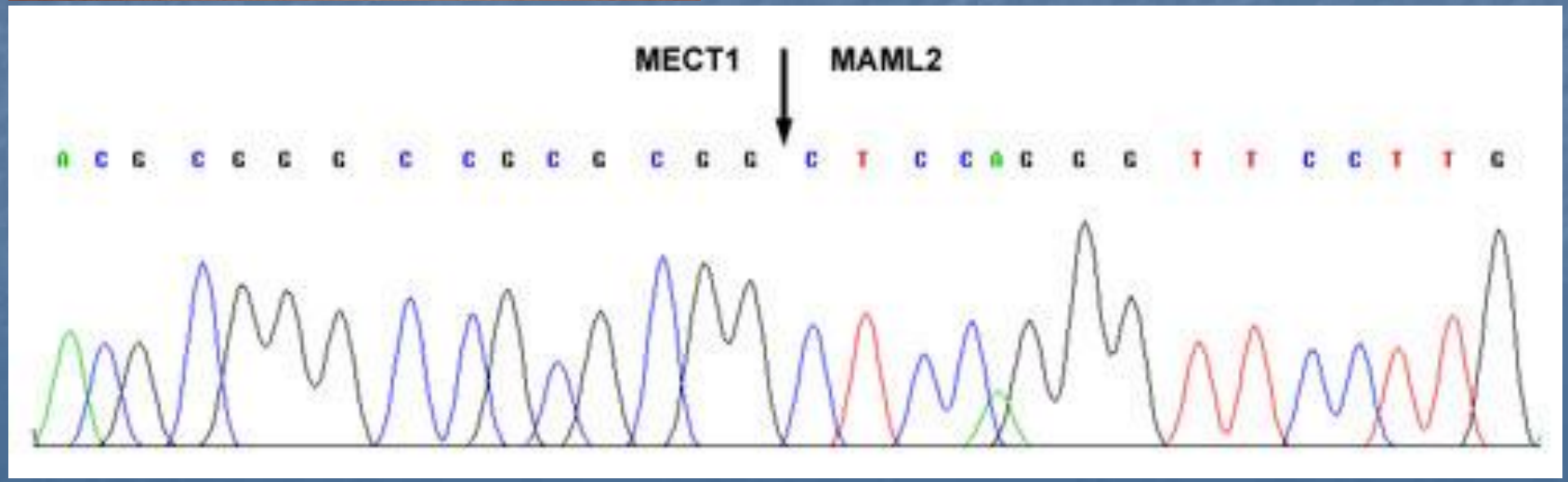
Update on molecular diagnostics of salivary gland tumors

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- NUT midline carcinoma
- Mammary analogue secretory carcinoma (MASC)

Mucoepidermoid carcinoma



- common malignant SG tumor
- broad age range, minor and major SG
- translocation *t(11;19)* specific for MEC
- *MECT1-MAML2* translocation
- FISH or RT-PCR analysis



Mucoepidermoid carcinoma

- Highly variable clinical prognosis
- Grading systems- AFIP, Brandwein
- Translocation *t(11;19)* fuses ***MECT1*** (*mucoepidermoid carcinoma translocated-1*) at 19p13 with ***MAML2*** (*mastermind-like gene family*) at 11q21
- Fusion positive patients have better outcomes
  - Less local recurrences, metastases and tumor-related deaths

Histopathology 2011, **59**, 90–97. DOI: 10.1111/j.1365-2559.2011.03890.x

Impact of *CRTC1/3–MAML2* fusions on histological classification and prognosis of mucoepidermoid carcinoma

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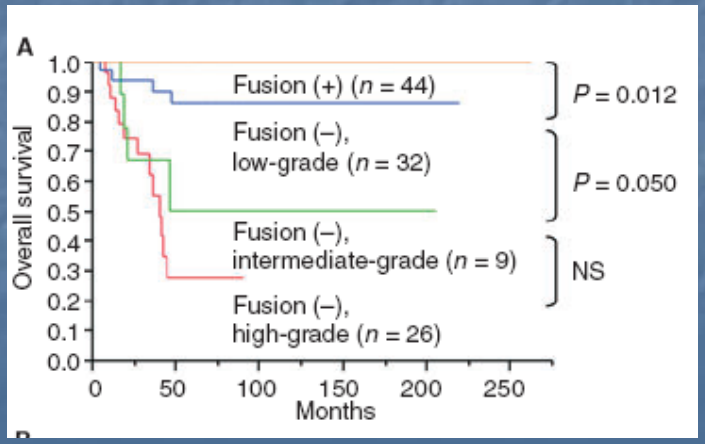
- Fusion positive cases of MEC have better outcome even in high grade morphology



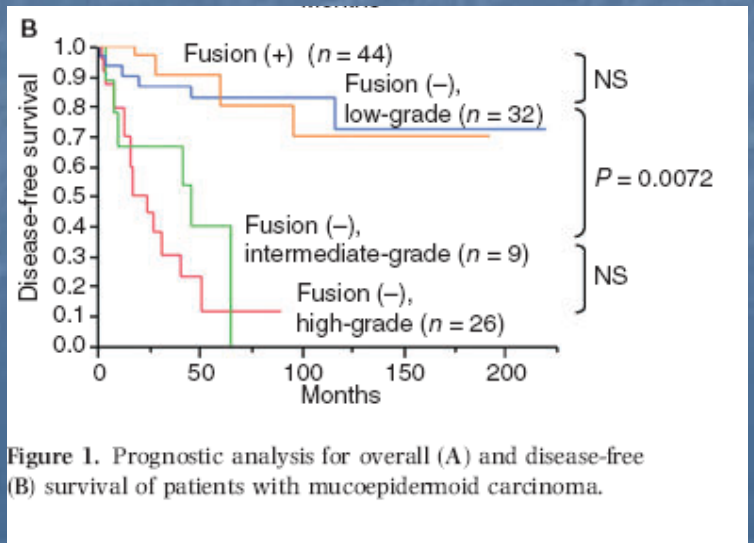


Figure 1. Prognostic analysis for overall (A) and disease-free (B) survival of patients with mucoepidermoid carcinoma.

MECT1-MAML2 translocation can be used in differential dg.

Oncocytic Mucoepidermoid Carcinoma

Clinicopathologic Description in a Series of 12 Cases

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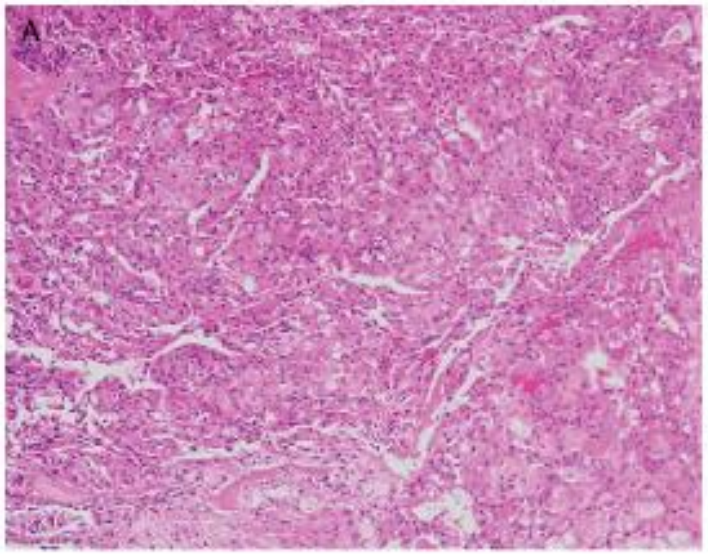
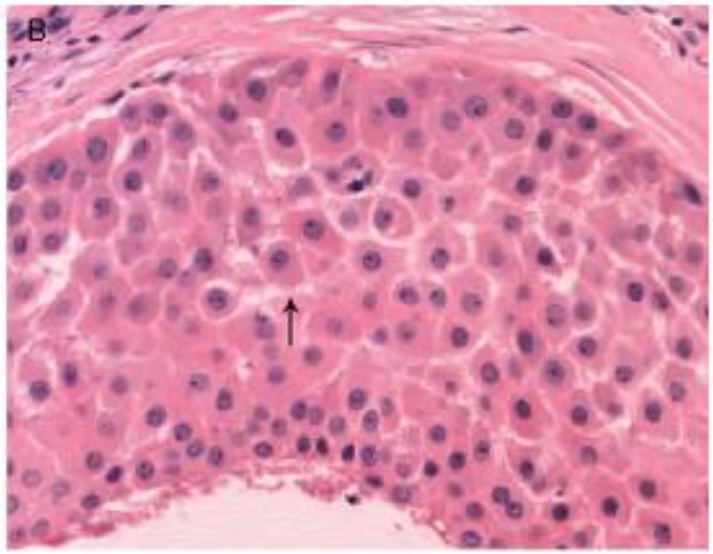
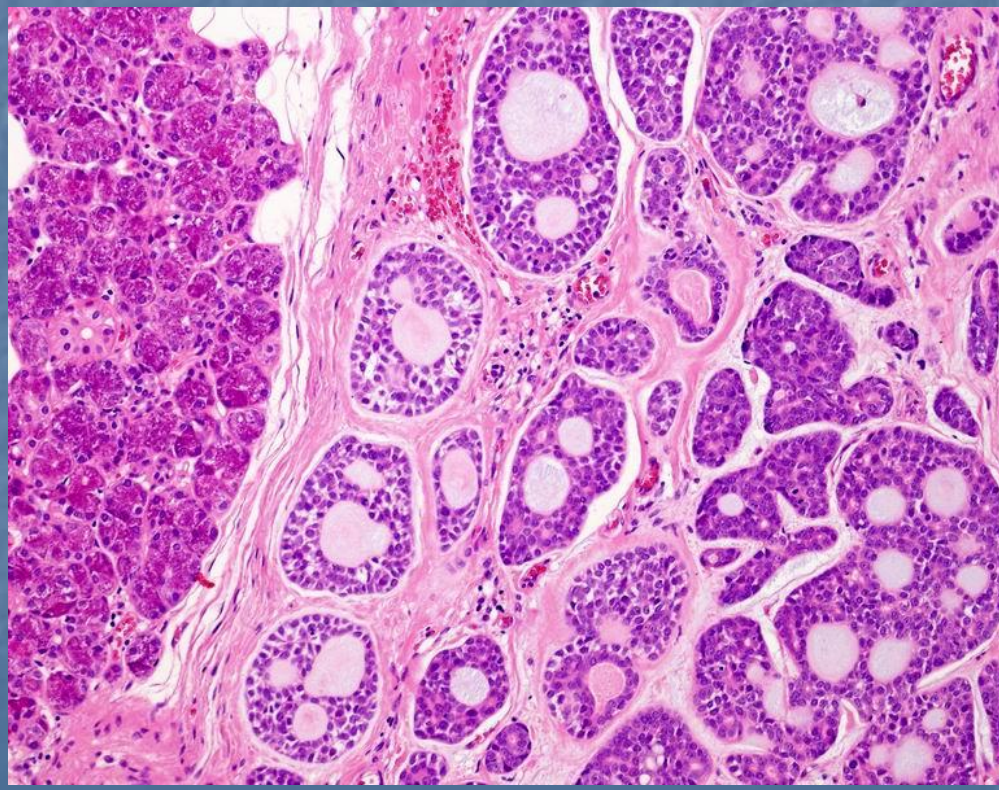
Am J Surg Pathol 2009:33:409-416





Adenoid cystic carcinoma

- both minor and major SG
- relentless clinical course with late recurrences and distant metastases
- c-KIT (CD117) over-expression
- No evidence of *c-KIT gene* mutations
  - Mixed results with imatinib which targets c-kit

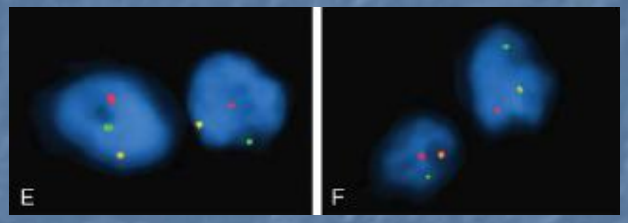


Adenoid cystic carcinoma

- Recurrent *t(6;9)* translocation in AdCC of both head and neck (salivary, lacrimal, ceruminal glands) and breast
- Translocation fuses *MYB oncogene* with transcription factor gene *NFIB*
  - Leads to chimeric *MYB-NFIB* fusion transcript
  - *MYB-NFIB* fusion is a candidate therapeutic target
  - MYB activation through gene fusion is a major oncogenic event in AdCCa of many sites

NUT Midline Carcinoma

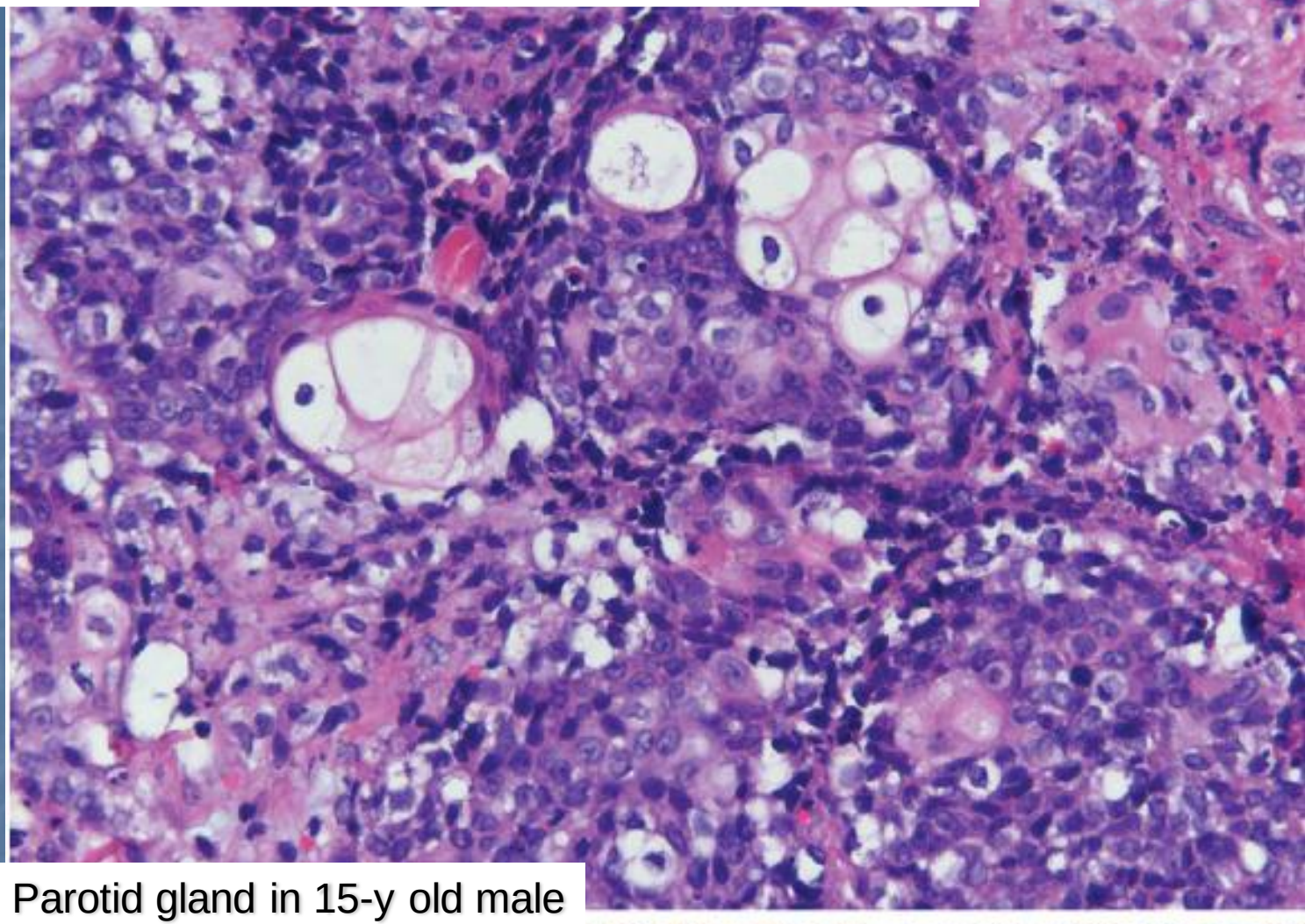
- New type of aggressive ca has been described, *t(15;19)(q14;p13.1)*
- Midline structures of head and neck in young adults
- Composed of undifferentiated basaloid cells with focal squamous differentiation



  - Dual color FISH analysis for NUT gene with splitting of green-red probe on tu cells
  - *BRD4* dual color FISH analysis

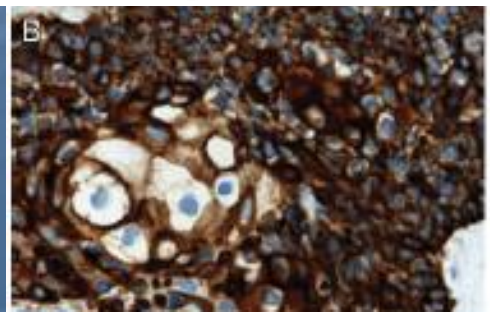
NUT ca

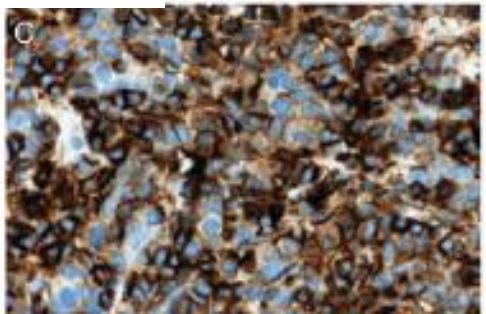
Bakker et al: Am J Surg Pathol 2009:33:1253-1258

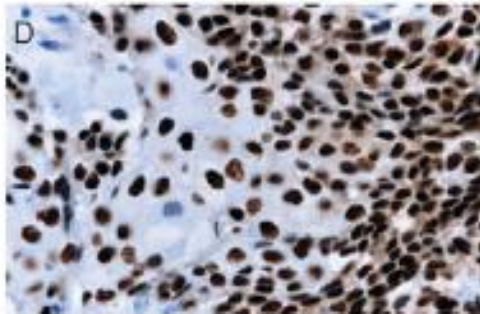


Parotid gland in 15-y old male

CAM 5.2+
CD56+
p63+

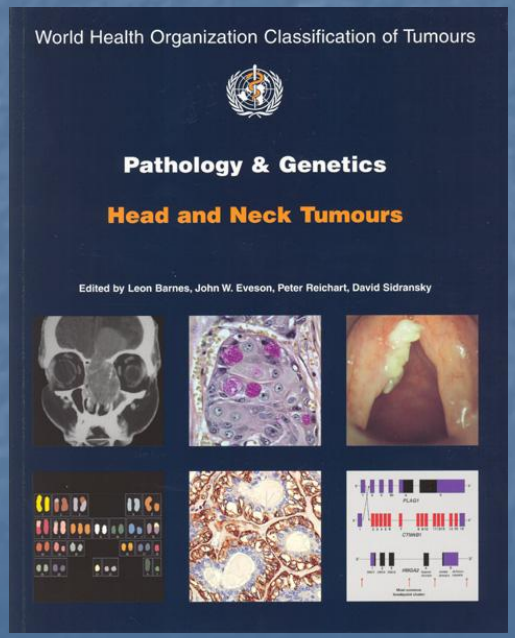






Newly recognized entities

- Mammary analogue secretory carcinoma
- Sclerosing polycystic adenosis
- Cribriform adenocarcinoma, tongue type
- Keratocystoma



WHO 2005

Mammary Analogue Secretory Carcinoma of Salivary Glands, Containing the *ETV6-NTRK3* Fusion Gene: A Hitherto Undescribed Salivary Gland Tumor Entity

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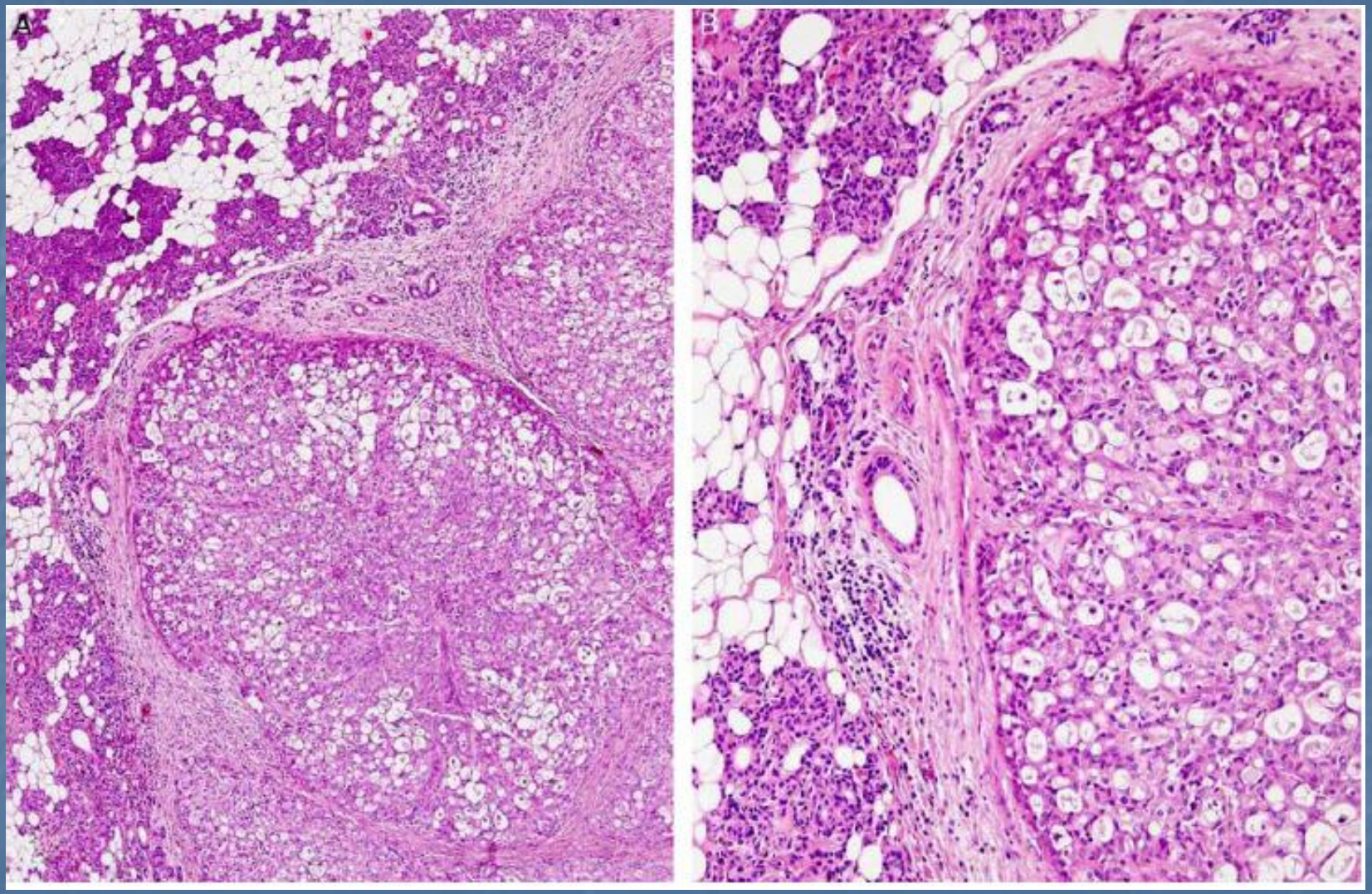
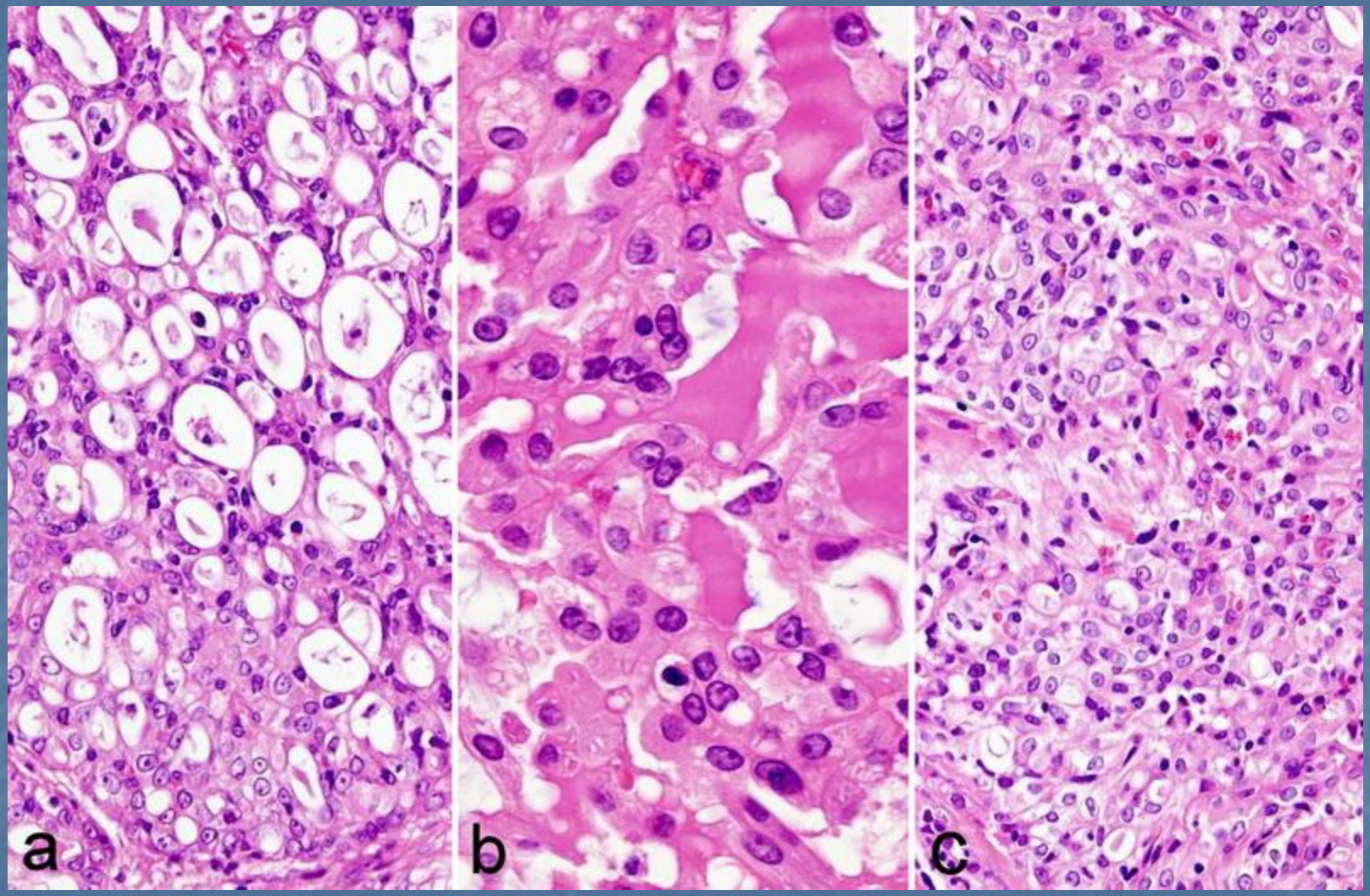
Abstract: We present a series of 16 salivary gland tumors with histomorphologic and immunohistochemical features reminiscent of secretory carcinoma of the breast. This is a hitherto undescribed and distinctive salivary gland neoplasm, with features resembling both salivary acinic cell carcinoma (AciCC) and low-grade cystadenocarcinoma, and displaying strong similarities to breast secretory carcinoma. Microscopically, the tumors have a lobulated growth pattern and are composed of microcystic and glandular spaces with abundant eosinophilic homogenous or bubbly secretory material positive for periodic acid-Schiff, mucicarmine, MUC1, MUC4, and mammaglobin. The neoplasms also show strong vimentin, S-100 protein, and STAT5a positivity. For this tumor, we propose a designation mammary analogue secretory carcinoma of salivary glands (MASC). The 16 patients comprised 9 men and 7 women, with a mean age of 46 years (range 21 to 75). Thirteen cases occurred in the parotid gland, and one each in the minor salivary glands of the buccal mucosa, upper lip, and palate. The mean size of the tumors was 2.1 cm (range 0.7 to 5.5 cm). The duration of symptoms was recorded in 11 cases and ranged from 2 months to 30 years. Clinical follow-up was available in 13 cases, and ranged from 3 months to 10 years. Four patients suffered local recurrences. Two patients died, 1 of them owing to multiple local recurrences with extension to the temporal bone, and another owing to metastatic dissemination to cervical lymph nodes, pleura, pericardium, and lungs. We have shown a t(12;15) (p13;q25) *ETV6-NTRK3* translocation in all but one case of MASC suitable for analysis. One case was not analyzable and another was not available for testing. This translocation was not found in any conventional salivary AciCC (12 cases), nor in other tumor types including pleomorphic adenoma (1 case) and low-grade cribriform cystadenocarcinoma (1 case), whereas *ETV6-NTRK3* gene rearrangements were proven in all 3 tested cases of mammary secretory carcinoma. Thus, our results strongly support the concept that MASC and AciCC are different entities.

Key Words: salivary gland, acinic cell carcinoma, secretory carcinoma, mammary type, molecular pathology, *ETV6-NTRK3* translocation

(*Am J Surg Pathol* 2010;34:599–608)



Mammary analogue secretory carcinoma of salivary glands


a
b
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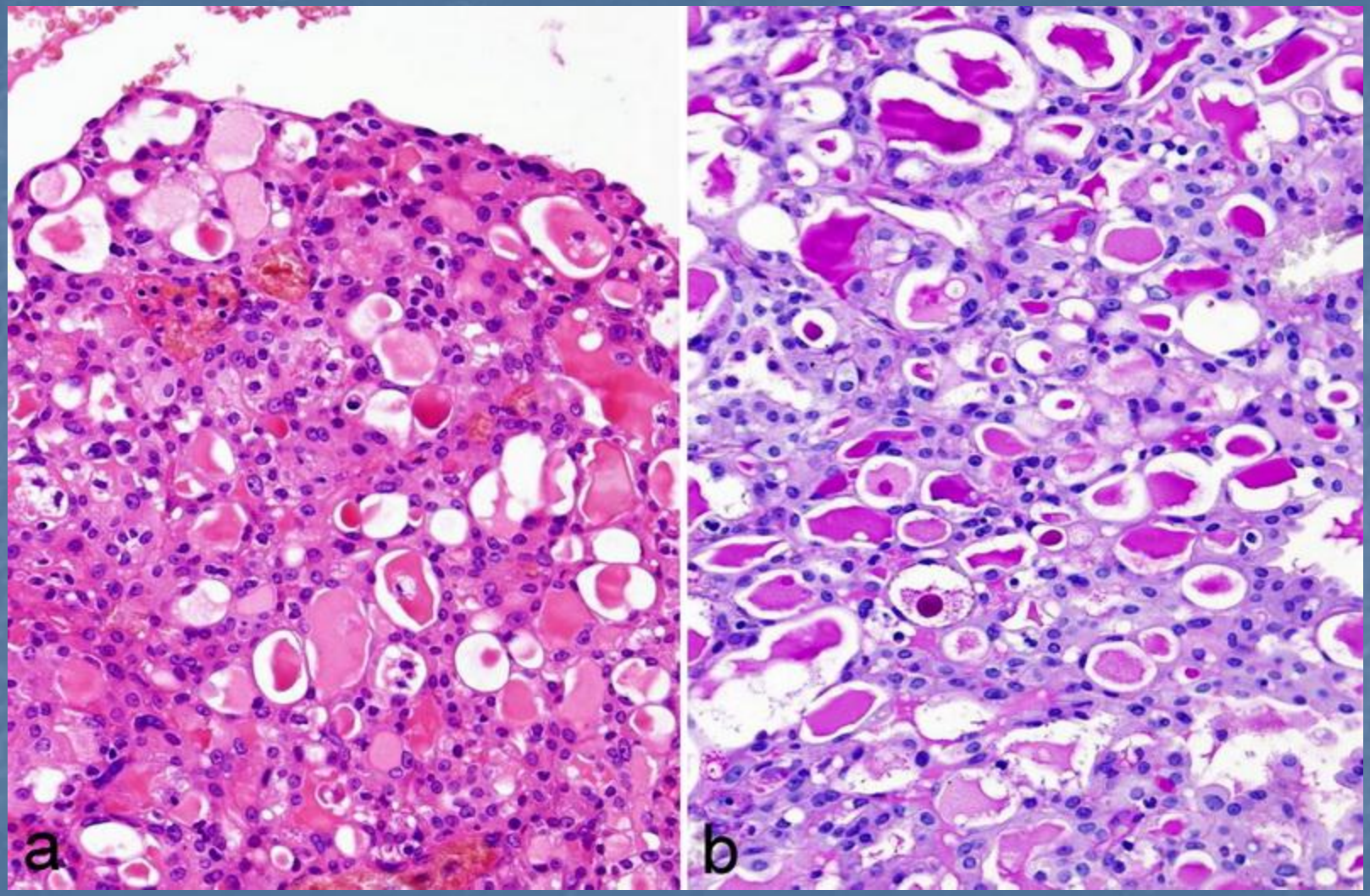
a
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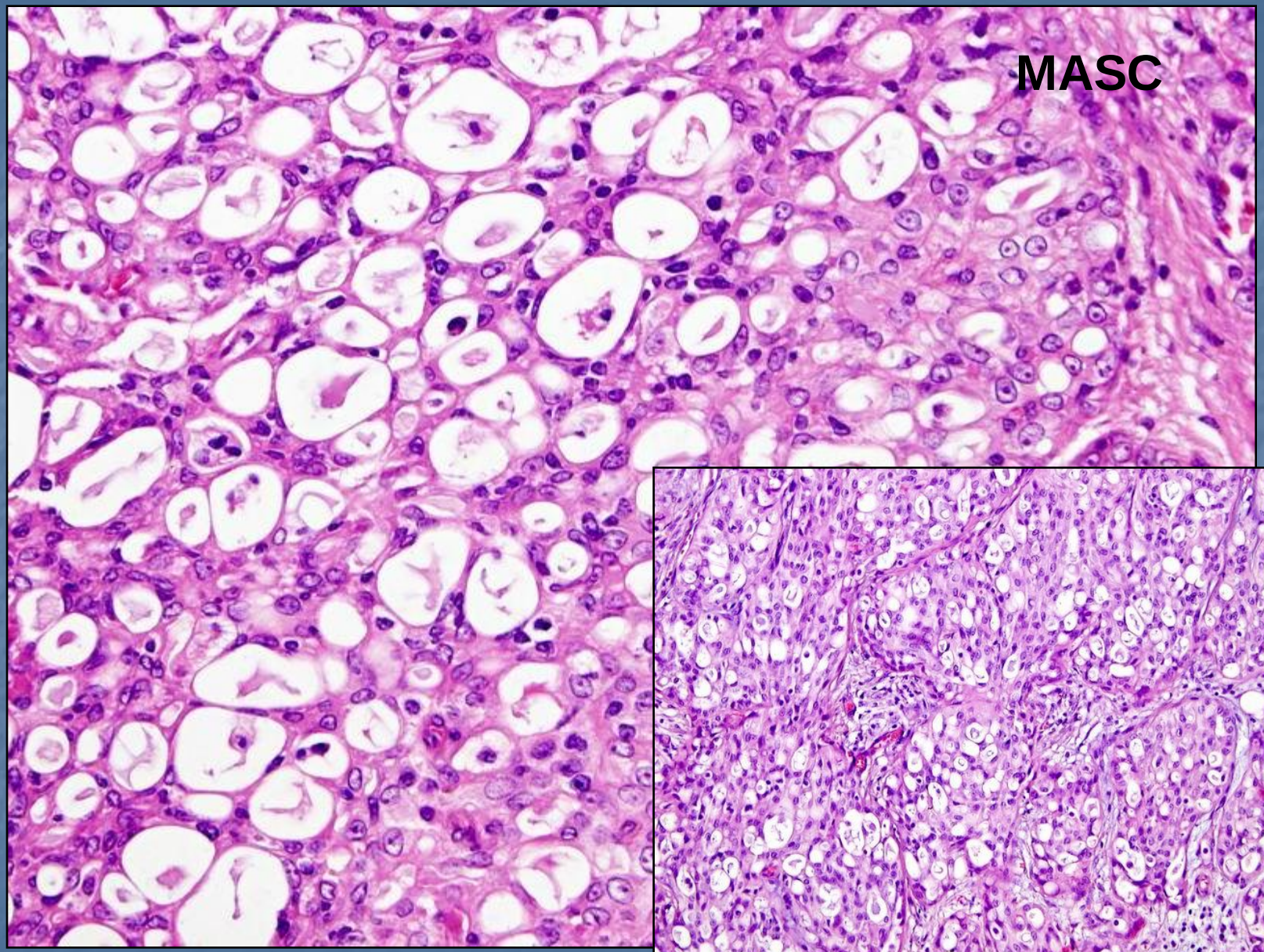
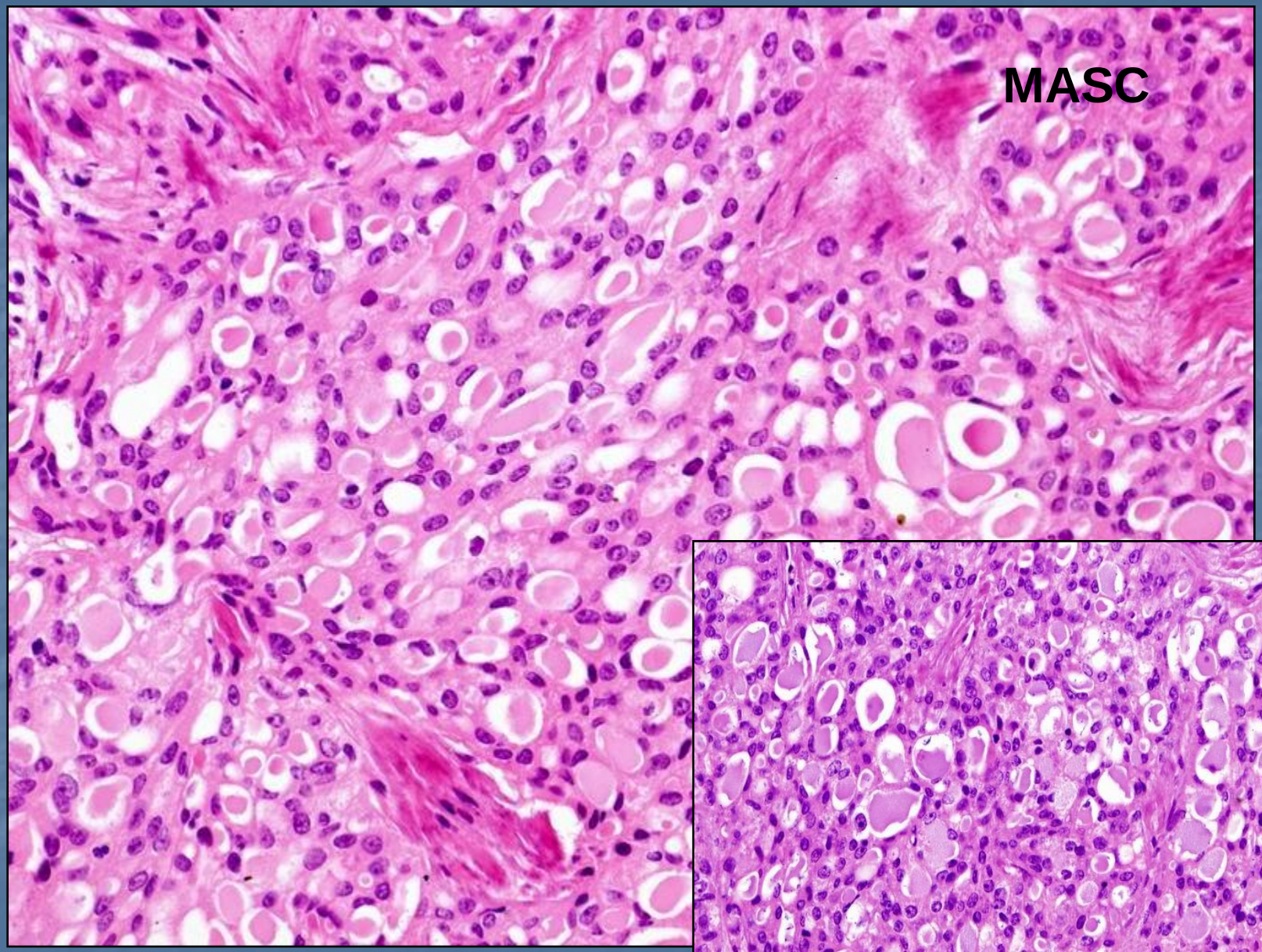

MASC
Secretory ca breast


MASC

Secretory ca of breast

World Journal of Surgical Oncology

BioMed Central

Case report

Open Access

Secretory carcinoma of the breast containing the ETV6-NTRK3 fusion gene in a male: case report and review of the literature

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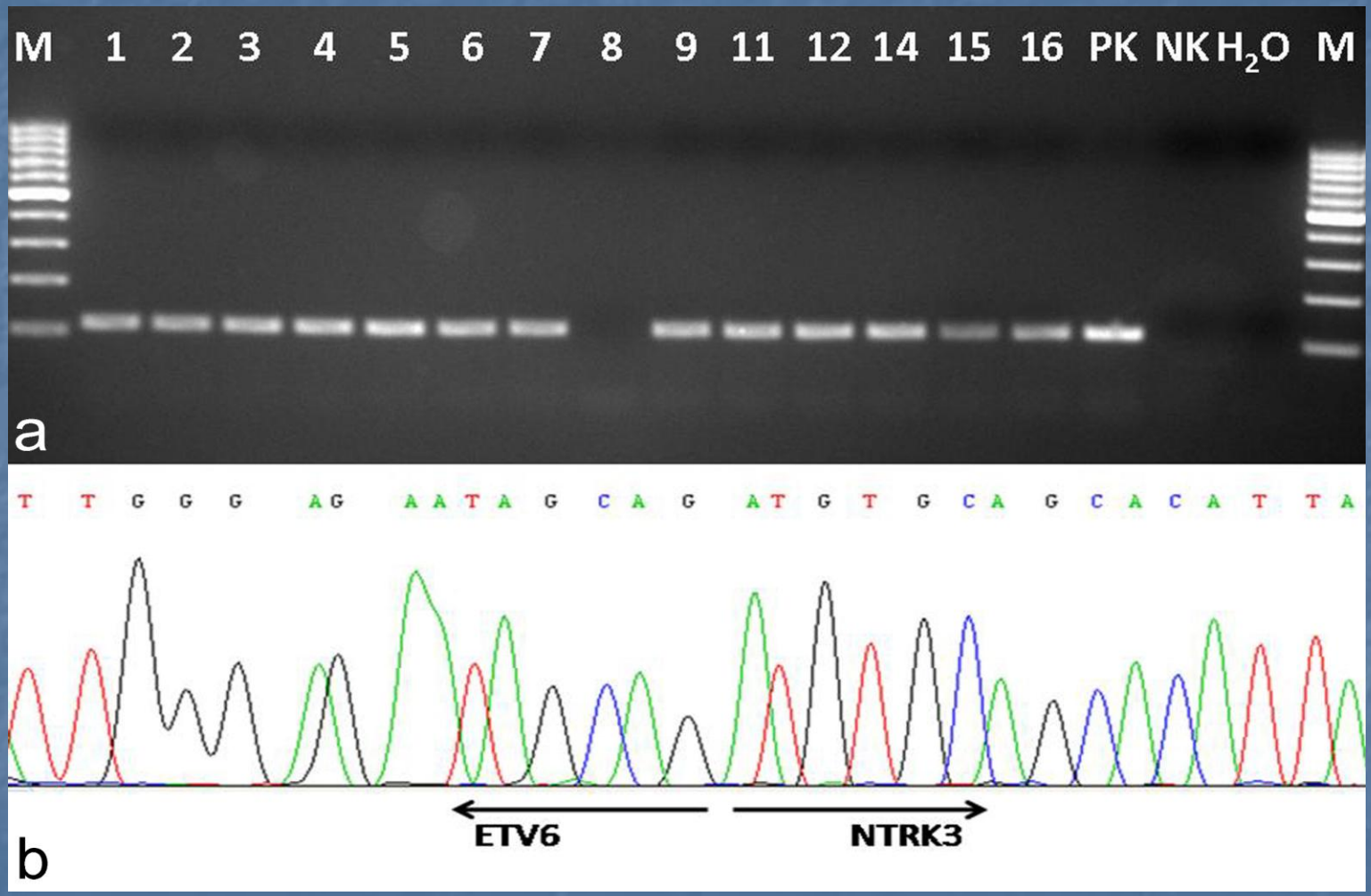
-secretory carcinoma of breast is associated with t(12;15)(p13;q25) ETV6-NTRK3 translocation

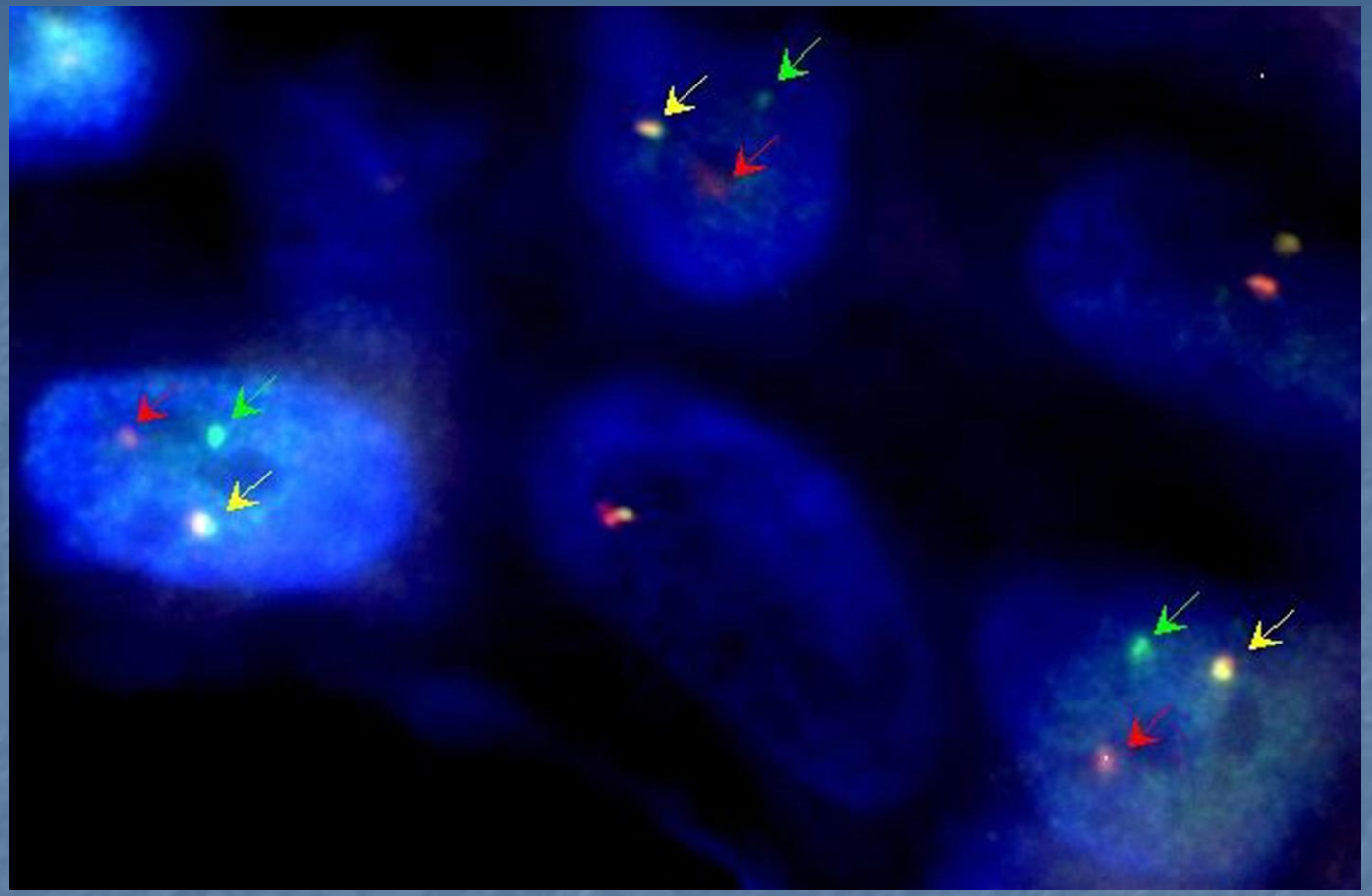
-fusion gene first recognized in congenital fibrosarcoma

-in mammary lesions relatively specific for SC

Sequence analysis of ETV6-NTRK3 gene fusion



Expression of ETV6-NTRK3 fusion transcript in the MASC and breast positive controls by RT-PCR. 1-16: Cases of MASC, PK-positive amplification control, NK-negative amplification control, H_2O – water. **Arrows show translocation breakpoint**



FISH analysis using LSI ETV6 (TEL) (12p13) Dual Color, Break Apart Rearrangement Probe (VYSIS/Abbott).
Green and red arrows show split signals indicating break of ETV6 gene. Yellow arrows show nonaltered chromosome.

No break of ETV6 gene in 14 salivary gland tu with secretory-like morphology

MASC

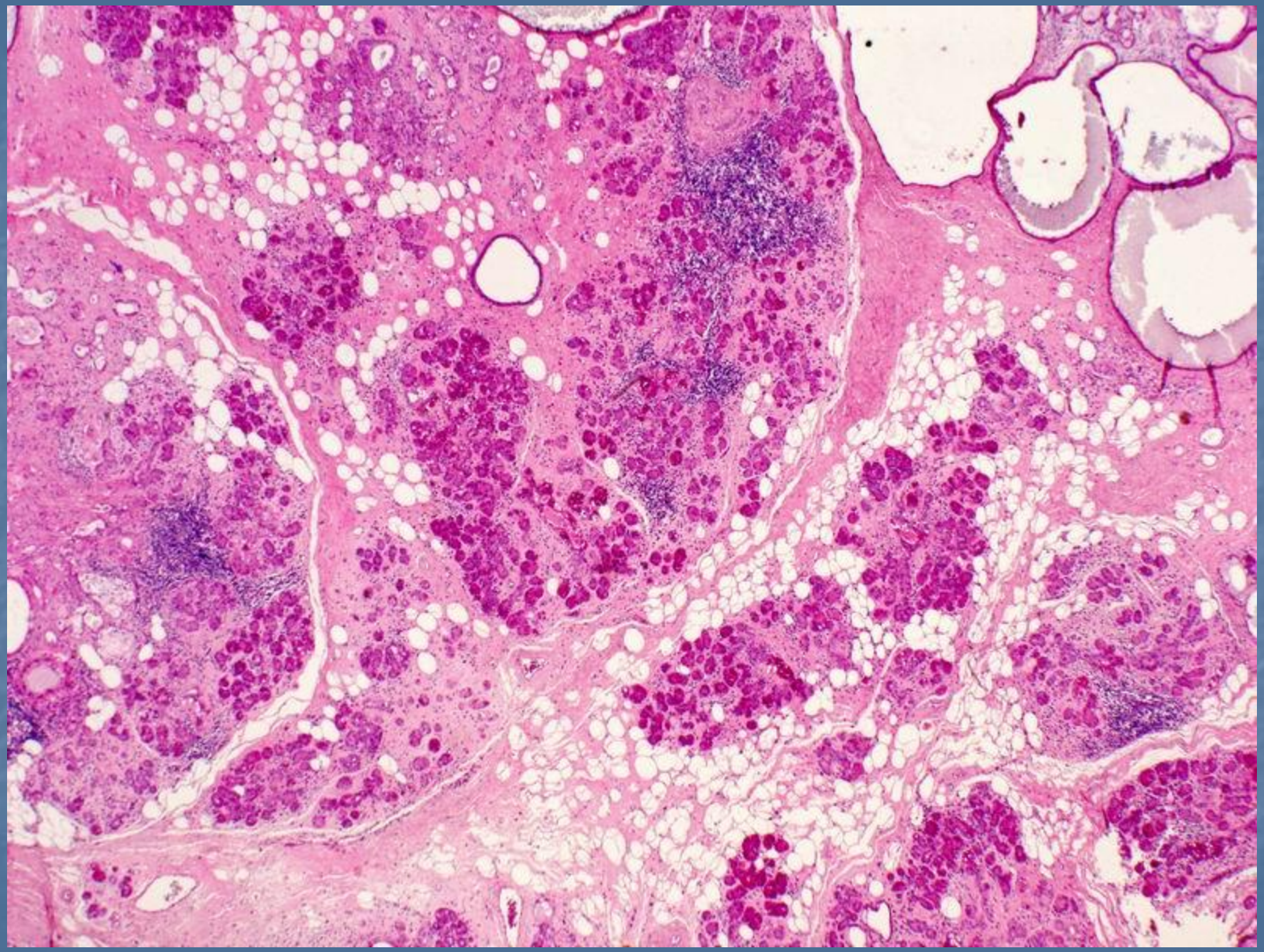
- distinctive salivary gland tumor (S100+) resembling breast secretory carcinoma
- ETV6-NTRK3 gene rearrangements demonstrated in MASC, not in AciCC
- MASC and salivary AciCC are distinct entities and should be recorded separately in salivary gland tumor classifications

Sclerosing polycystic adenosis

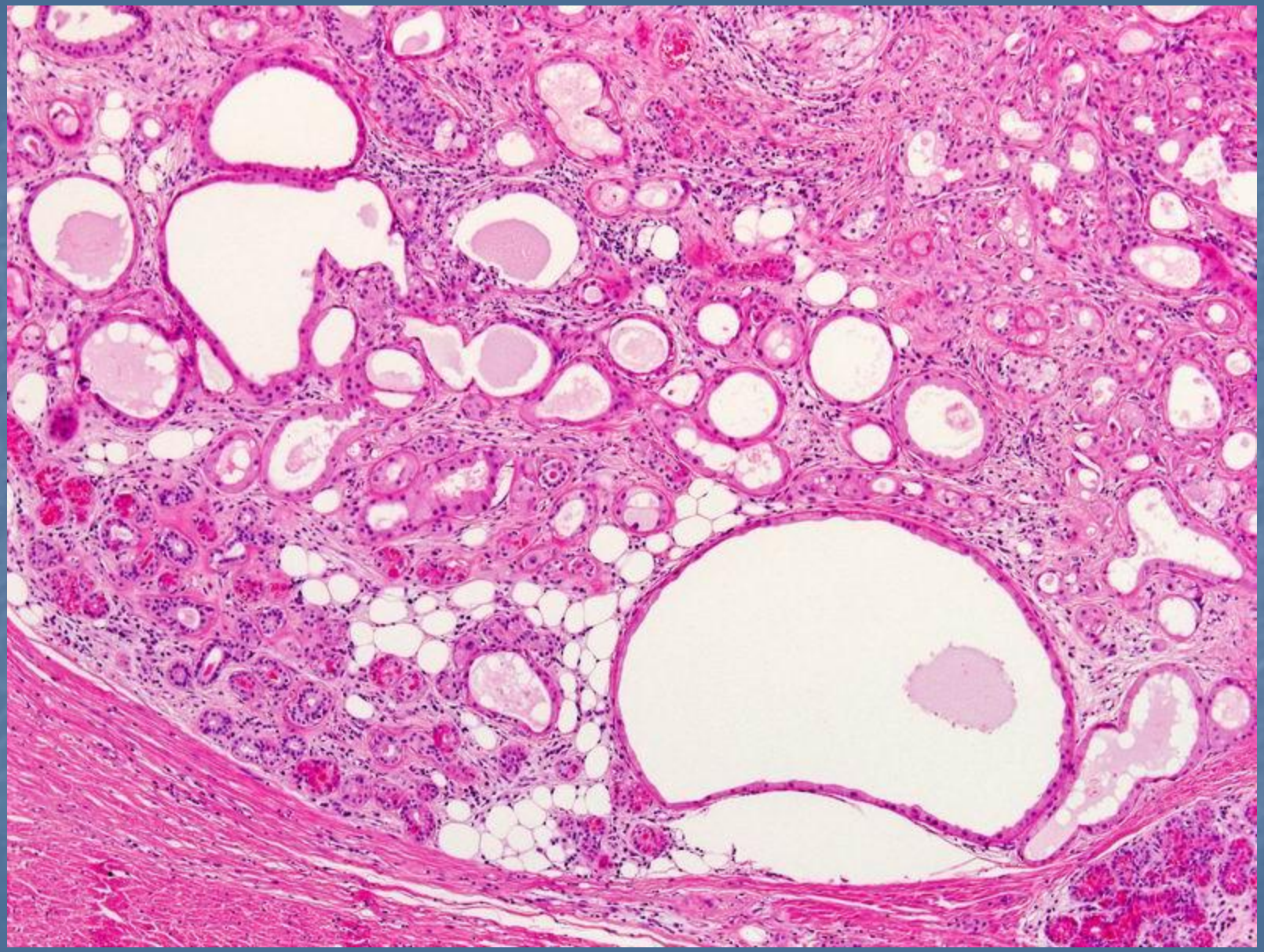
With recent molecular evidence supporting its neoplastic nature

Sclerosing Polycystic Adenosis

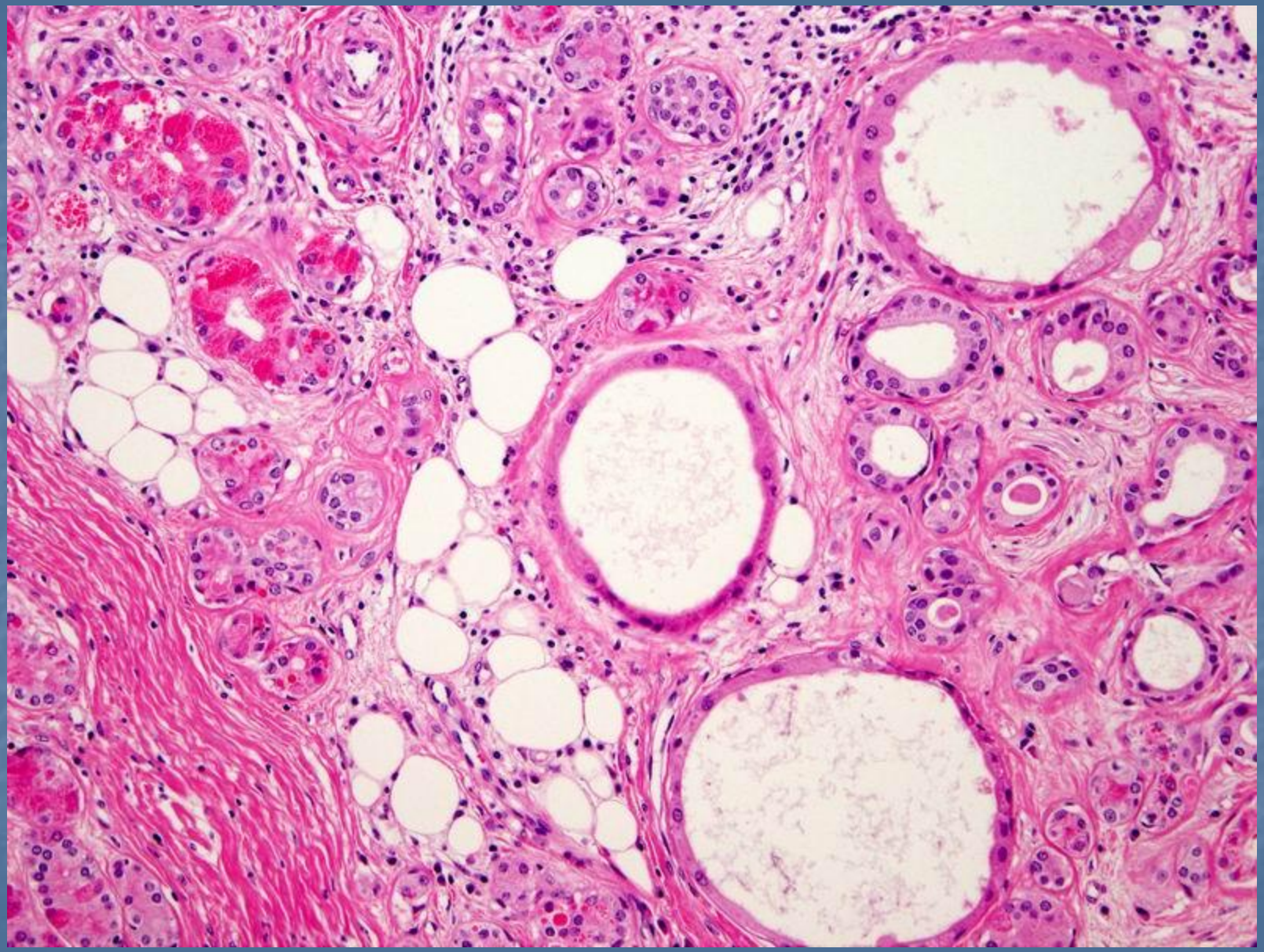
- is rare distinctive neoplastic lesion of the major salivary glands
- lesion resembles FCD/adenosis tumor of breast
- originally considered a sclerosing inflammatory pseudoneoplastic process
- it represents a true neoplastic condition characterized by clonality, focal dysplasia, and a tendency to recur



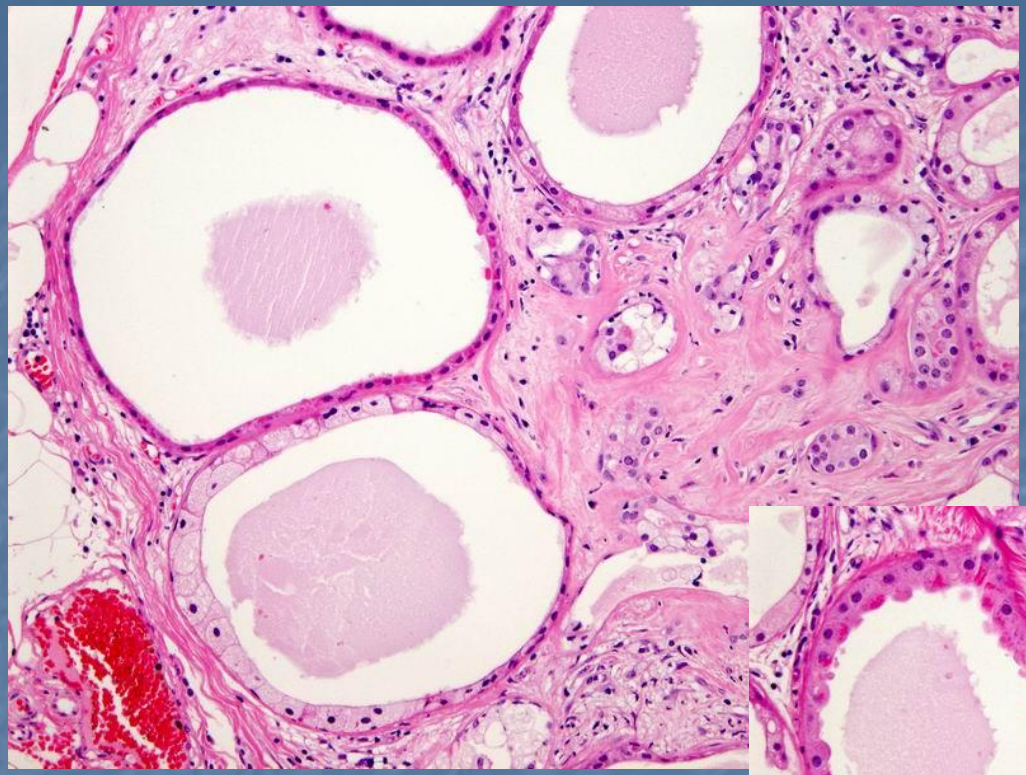
Sclerosing polycystic adenosis

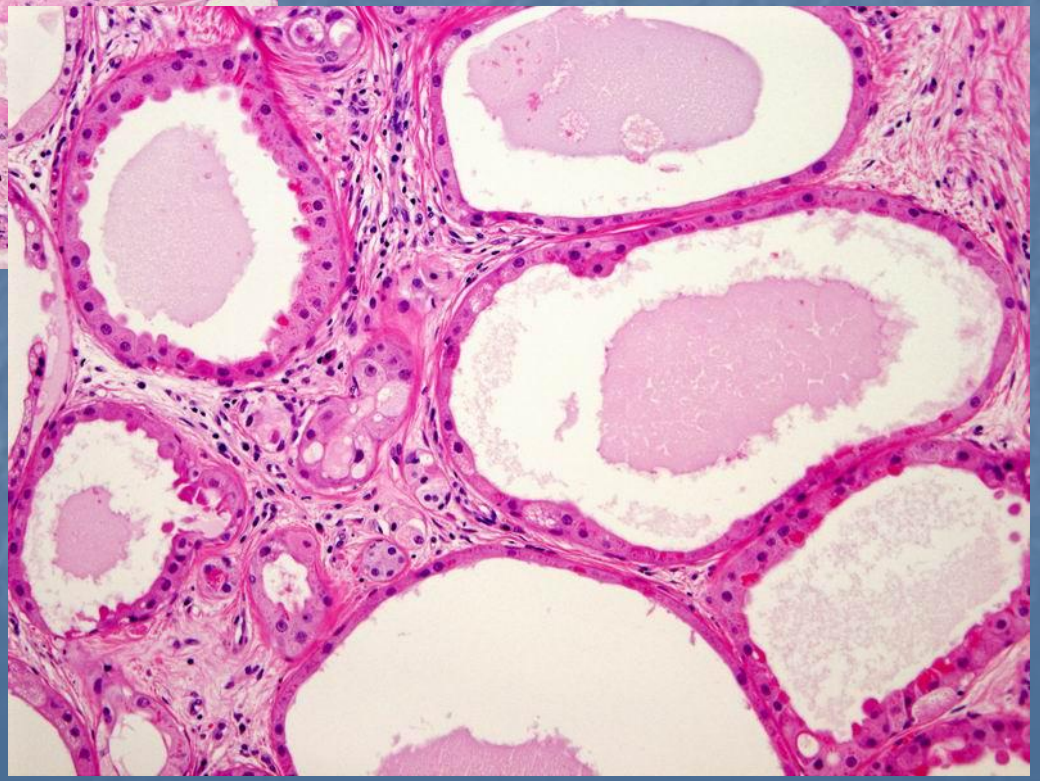


Sclerosing polycystic adenosis



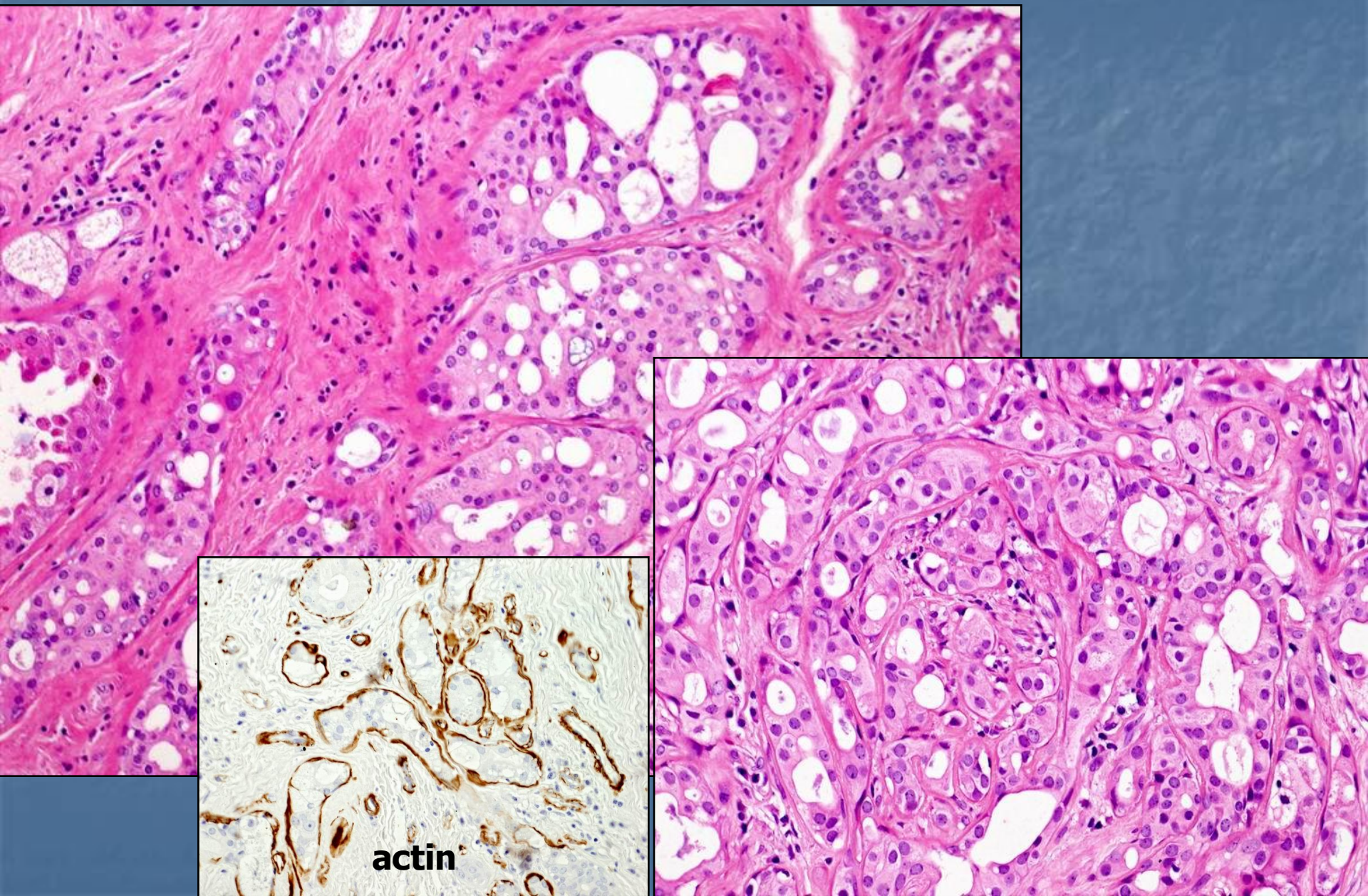
Sclerosing polycystic adenosis





Sclerosing polycystic adenosis

Variable degrees of hyperplasia and dysplasia



Clonal Nature of Sclerosing Polycystic Adenosis of Salivary Glands Demonstrated by Using the Polymorphism of the Human Androgen Receptor (HUMARA) Locus as a Marker

Alena Skálová, MD, Douglas R. Gnepp, MD,† Roderick H. W. Simpson, MB CHB, FRCPath,‡ Jean E. Lewis, MD,§ Dirk Janssen, MD,¶ Radek Sima, MSc,** Tomas Vanecek, MSc,** Silvana Di Palma, MD,†† and Michal Michal, MD**

Abstract: Sclerosing polycystic adenosis (SPA) is a recently described, rare lesion of the salivary glands that bears a resemblance to epithelial proliferative lesions of the breast. The true nature of the lesion is unknown, but up to now it has been generally believed to represent a pseudoneoplastic sclerosing and inflammatory process. However, local recurrence developed in about one-third of the cases. Superimposed dysplastic changes ranging from low-grade dysplasia to carcinoma in situ were described in SPA. Although no metastases-related and/or disease-related patient deaths were documented, these clinical and histopathologic features raise the possibility that SPA might represent a neoplastic lesion. Polymorphism of the human androgen receptor locus is most frequently used to assess whether the pattern of X-chromosome inactivation is random or nonrandom, the latter strongly indicating clonality. In this study, the assay was applied to tissue from 12 examples of SPA. Three cases (males) were noninformative and 3 cases (females) could not be analyzed owing to poor quality of DNA, but all the remaining 6 lesions satisfied the criteria for monoclonality. We therefore conclude that the findings in the present study are further supporting evidence that SPA is a neoplasm, and not just a reactive process.

Key Words: sclerosing polycystic adenosis, salivary gland, clonality, HUMARA, dysplasia

(*Am J Surg Pathol* 2006;30:939–944)

a considerable histopathologic resemblance to fibrocystic disease of the breast.[20] It was first described in 1996 by Smith et al,[20] and to date, there have been approximately 40 cases reported in the world literature.[2–4,7,8,11,12,19,20] The true nature of the lesion is unknown, but it is generally believed to represent a pseudoneoplastic sclerosing and inflammatory process similar to proliferative and reactive changes well documented in benign fibrocystic disease of the breast.[3,4,20] Patients typically presented with slow growing mass, 4, in addition, had pain or sensation. Onset of symptoms ranged from 10 days to 2 years. One patient, in addition, had a history of chronic recurrent parotitis.[3] SPA has a distinct histologic growth pattern and frequently simulates carcinoma clinically and histologically. To date, none of the patients reported have developed metastases or died secondary to disease.

Recently, we reported 3 cases of SPA with hitherto undescribed superimposed atypical changes of the epithelium ranging in appearance from atypical hyperplasia to low-grade dysplasia and carcinoma in situ.[19] In addition, local recurrence has been described in about one-third of cases. Therefore, it is reasonable to question whether SPA might indeed represent a neoplastic lesion, perhaps even with a low-grade malignant potential.

To assess the clonality of female tissue samples, the pattern of inactivation of one of the 2 X chromosomes is most commonly used. In normal woman, 1 X chromo-

- Digestion of genomic DNA with methylation sensitive enzymes
- PCR amplification of CAG repeats at HUMARA locus at chromosome X

Clonality by HUMARA

spectrum of dysplastic changes ranging to DCIS

recurrences in 29% of cases

no meta, none died of disease

Cribriform adenocarcinoma of tongue
CAT

Histopathology 1999, 35, 495–501

Cribriform adenocarcinoma of the tongue: a hitherto unrecognized type of adenocarcinoma characteristically occurring in the tongue

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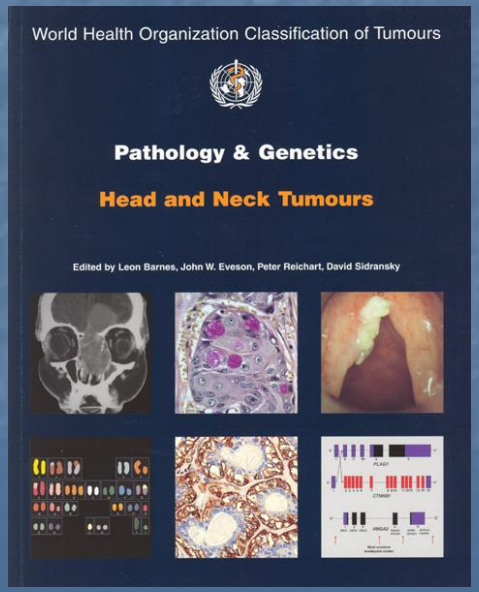
(1999) *Histopathology* 35, 495–501

Cribriform adenocarcinoma of the tongue: a hitherto unrecognized type of adenocarcinoma characteristically occurring in the tongue

"cribriform adenocarcinoma of tongue" CAT

- In 1999 we have described eight cases of an unusual carcinoma of the tongue
- infiltrating tumor with diverse growth patterns such as solid, microcystic, cribriform and papillary
- tumor cells are bland looking with uniform, often overlapping nuclei with ground-glass chromatin
- no significant mitotic activity, necrosis or hemorrhage

Possible variant of PLGA is CAT, but it is not yet clear whether this represents a genuine entity or just an unusual growth pattern in PLGA…….



WHO Classification of Tumours: Pathology and Genetics Head and Neck Tumours, IARC Press, 2005

Cribriform Adenocarcinoma of Minor Salivary Gland Origin Principally Affecting the Tongue: Characterization of New Entity

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Abstract: We present a series of 23 cases of a distinctive, hitherto poorly recognized low-grade adenocarcinoma, with several histologic features reminiscent of papillary carcinoma of the thyroid, and which mostly but not exclusively occurs in the tongue. All the tumors were unencapsulated and were divided into lobules that were composed mainly of cribriform and solid growth patterns. Therefore, we propose the name "cribriform adenocarcinoma of minor salivary gland origin (CAMSG)." All the patients were adults with a mean age at diagnosis of 55.8 years (range, 25 to 85 y). Fourteen of the 23 tumors were localized in the tongue, 3 in the soft palate, 2 in the retromolar buccal mucosa, 3 in the lingual tonsils, and 1 in the upper lip. Fifteen patients of 23 had synchronous metastases in the cervical lymph nodes at the time of diagnosis, bilateral in 3 cases. In 3 patients, the nodal metastasis was the first evidence of disease, later investigation revealing primary neoplasms in the base of tongue and tonsil, respectively. In addition, 1 patient developed a cervical lymph node metastasis 8 years after excision of a primary tumor of the tongue. Data on treatment and follow-up were available in 14 cases. The patients were treated by radical excision with clear margins (12 cases) or by simple excision (2 cases). Neck dissection was performed in 10 patients; 9 received radiotherapy, but none were treated by chemotherapy. Clinical follow-up ranged from 2 months to 13 years (mean, 6 y and 5 mo). Twelve patients are alive with no evidence of recurrent or metastatic disease after treatment, 1 patient died 2 years after surgery without evidence of tumor, and 1 patient is alive with recurrent tumor of the palate.

Key Words: cribriform adenocarcinoma of minor salivary glands, tongue, polymorphous low-grade adenocarcinoma, PLGA, myoepithelial cells, hybrid secretory and myoepithelial cells

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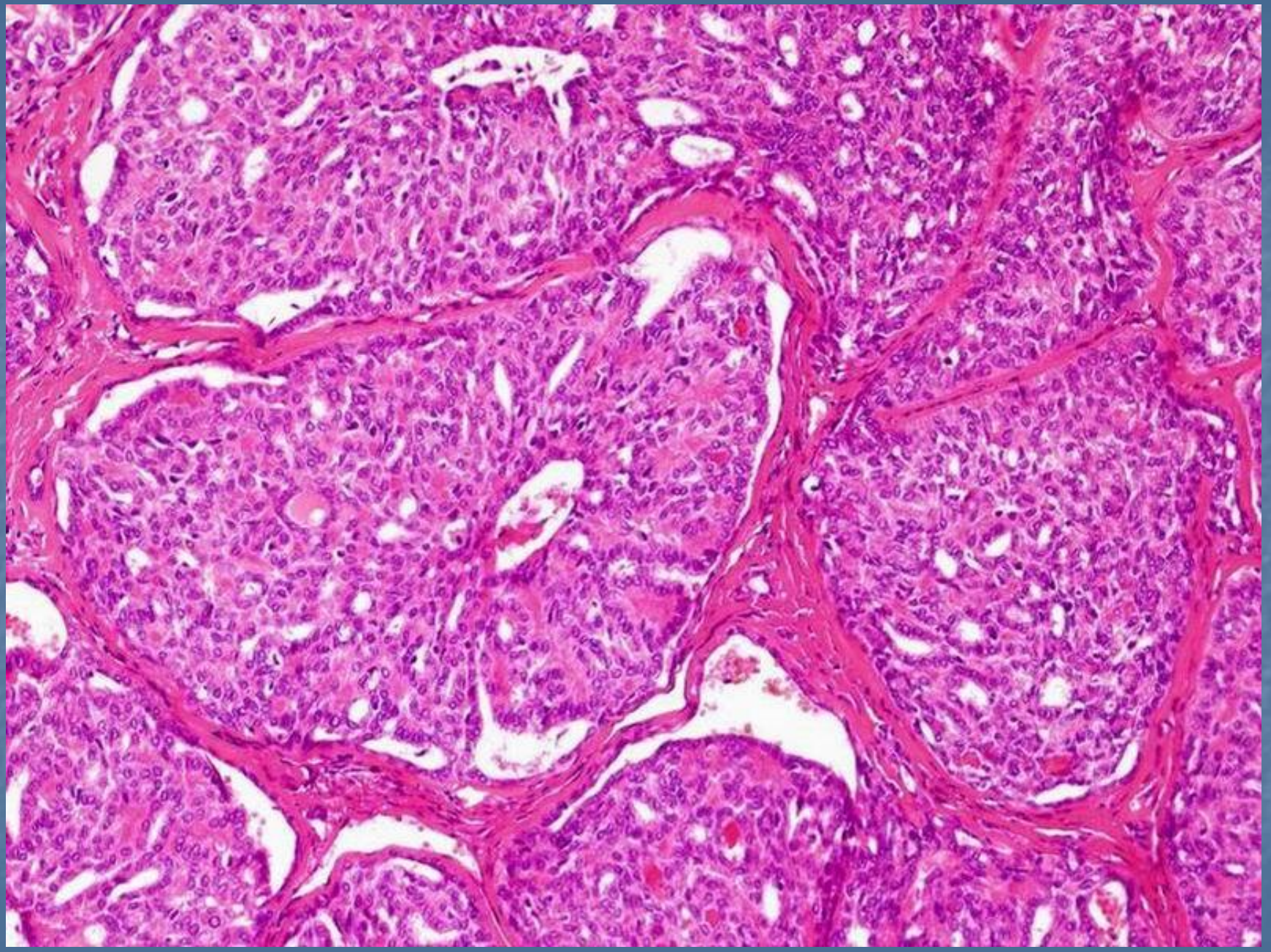
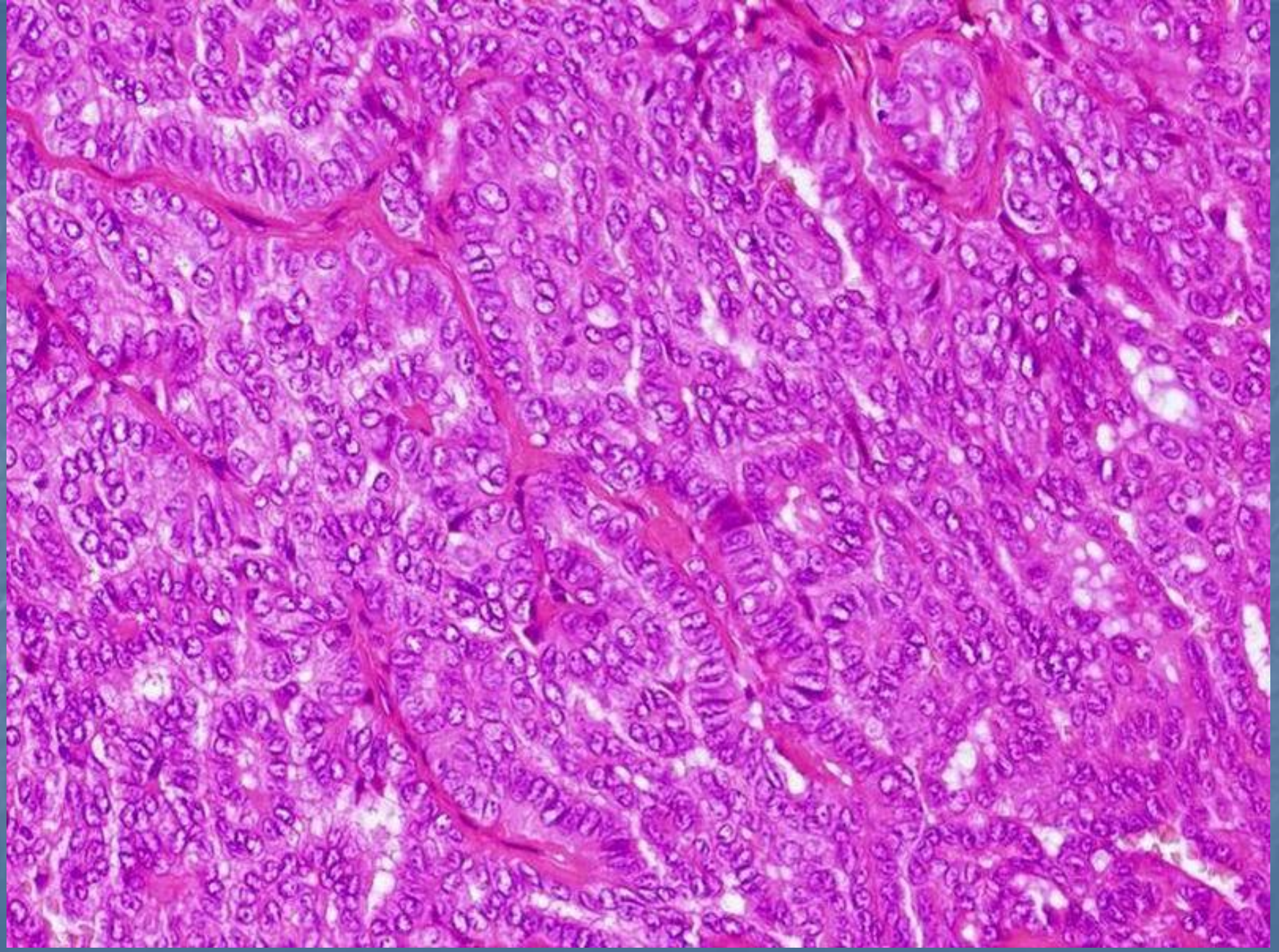
21 cases of CAT retrieved from salivary gland tumor registry:

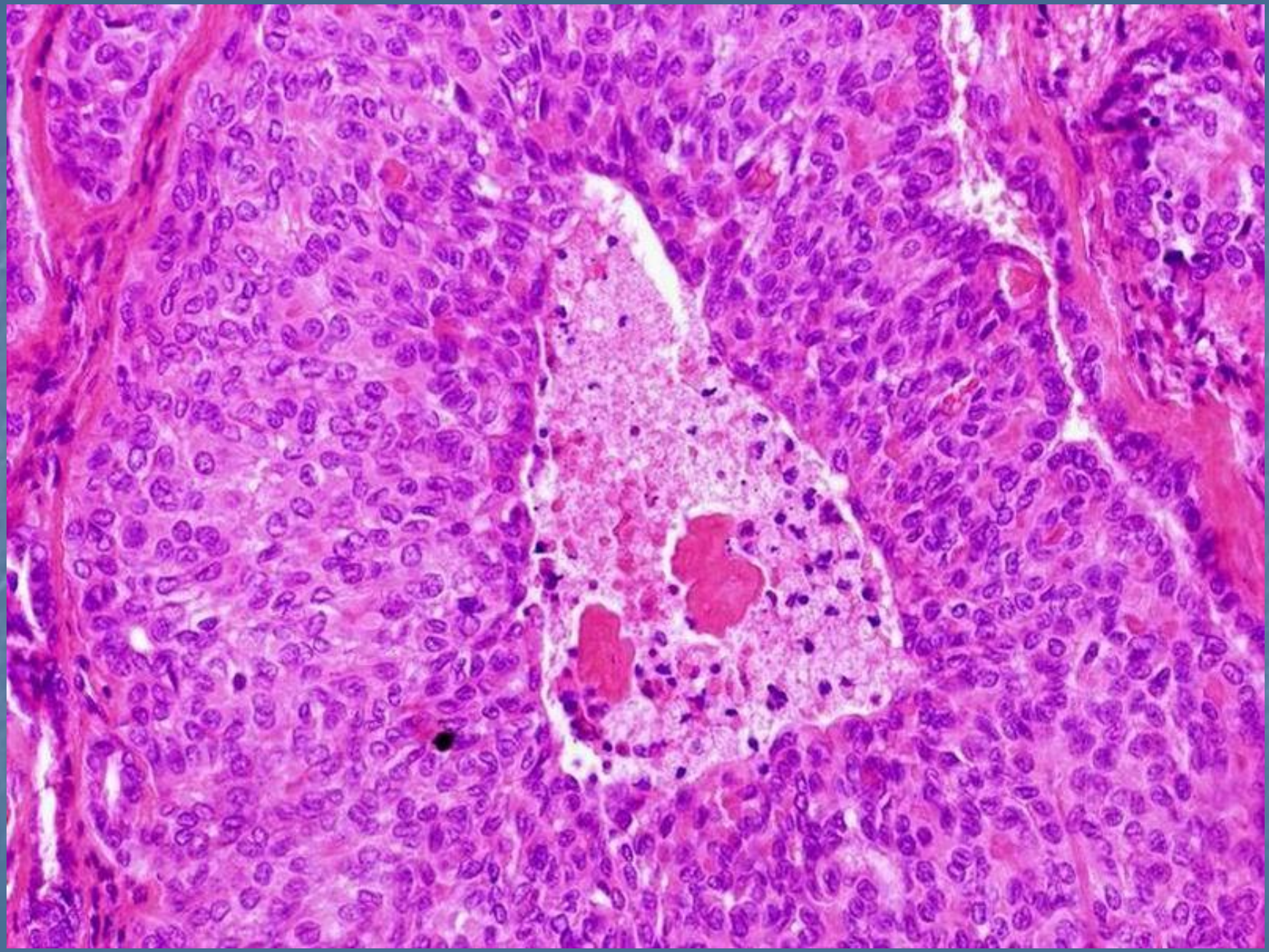
- most cases presented in the base of tongue (13) or/and in the tonsils (2)
- followed by palate (4), lip (1), and retromolar mucosa (1)



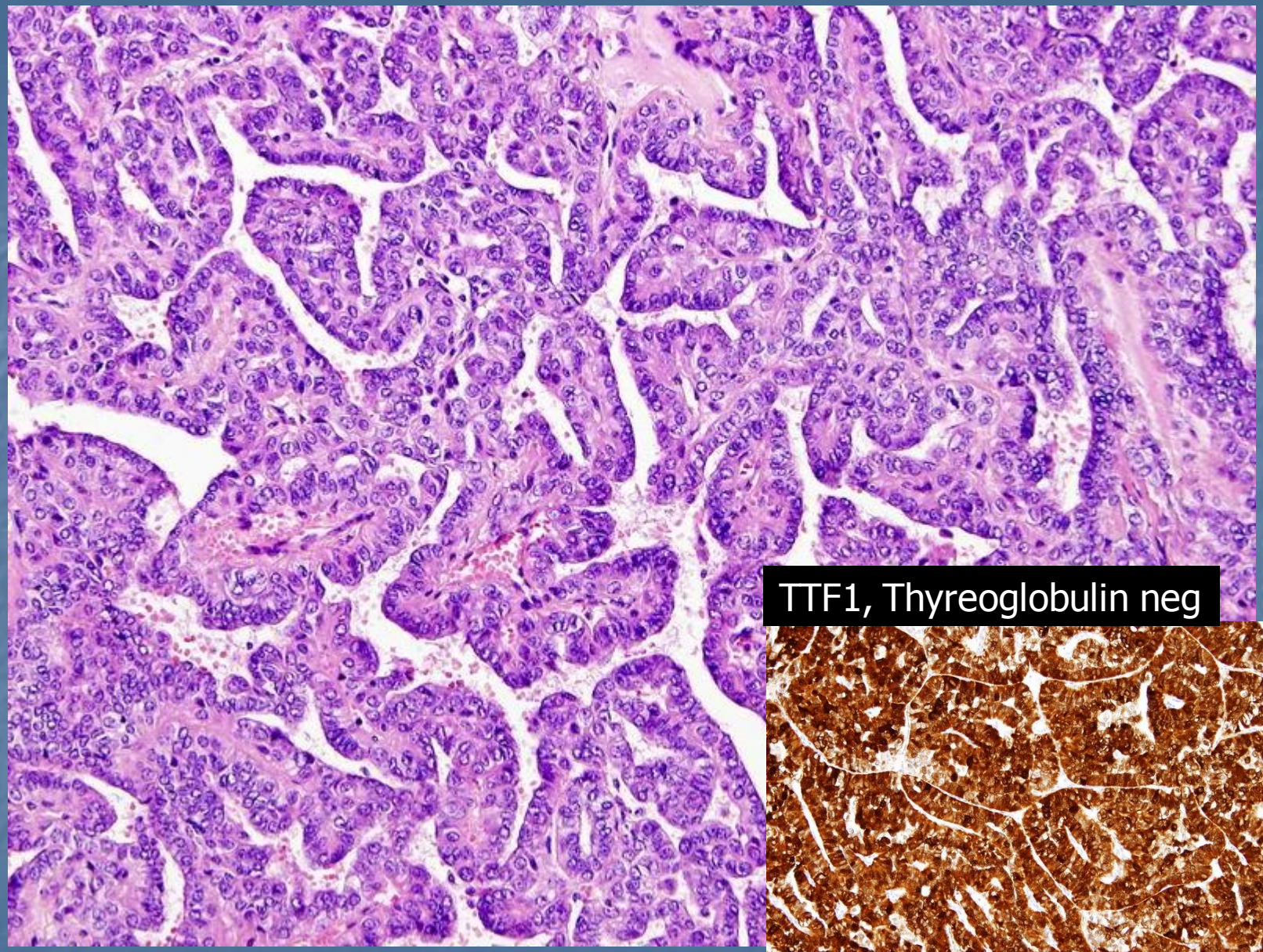
Cribriform and tubular structure



Ground-glass nuclei („Orhan Annie eyes“)-resemble papillary ca of thyroid



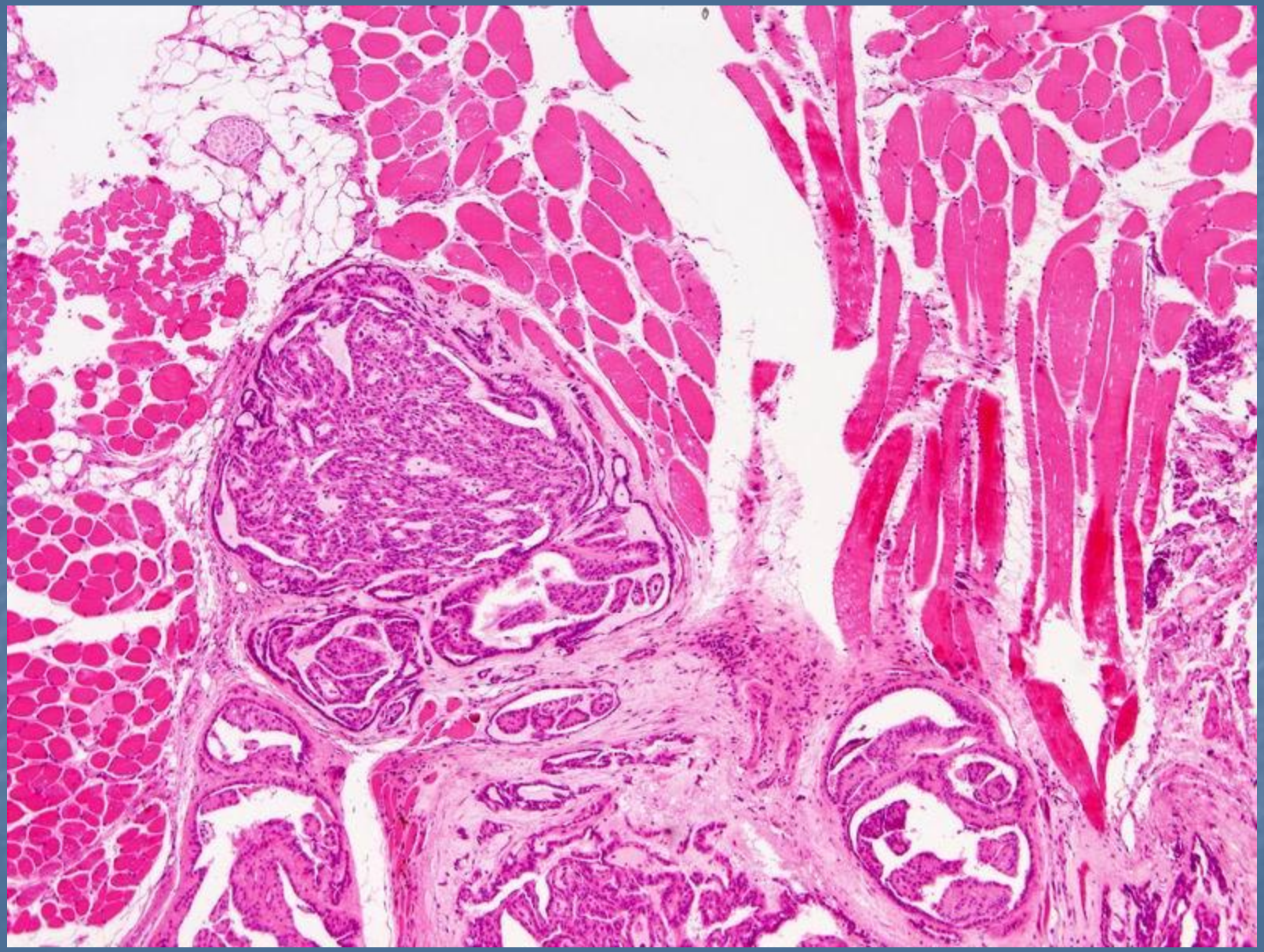
Peripheral palisading and arteficial clefts



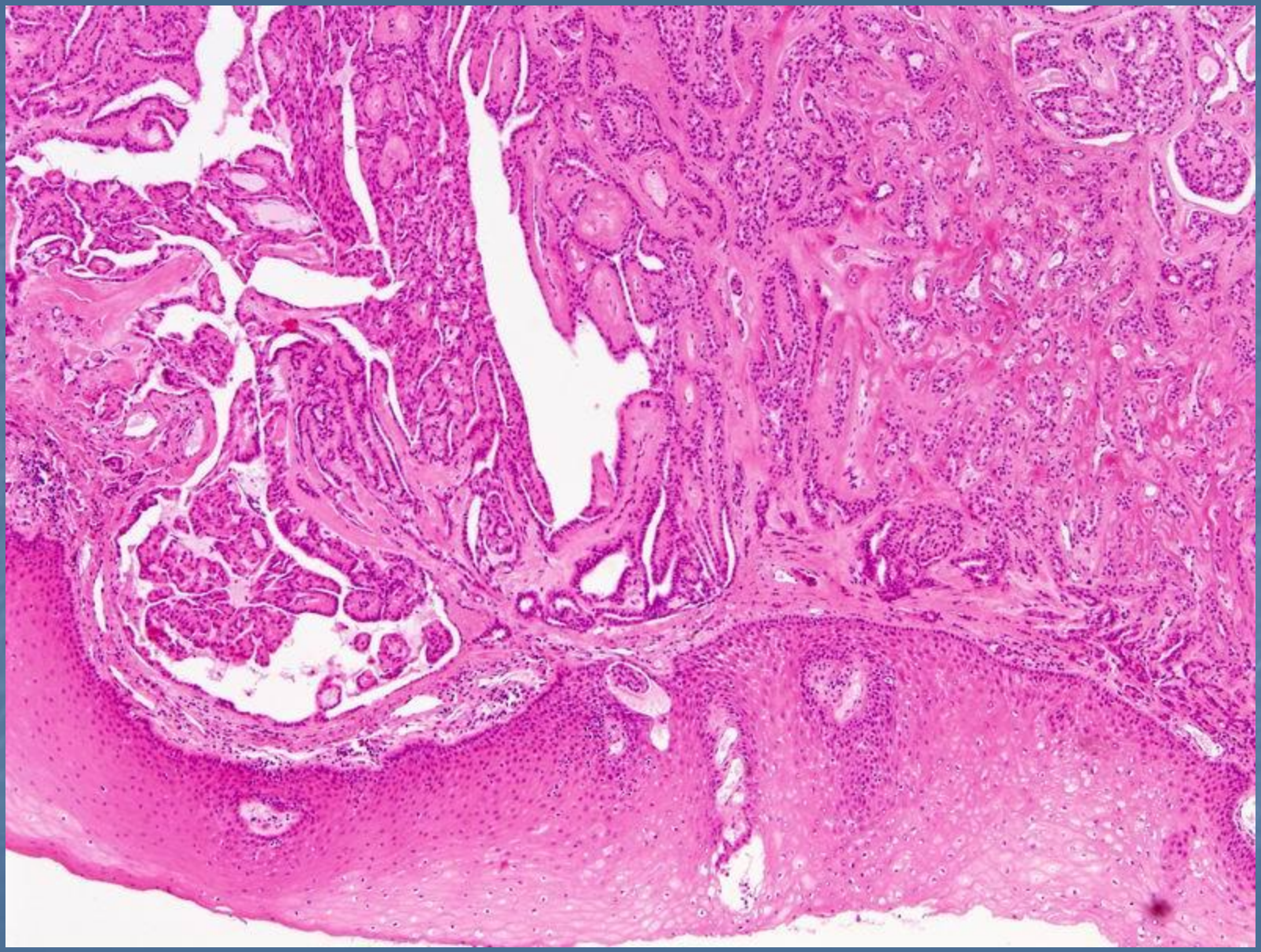
TTF1, Thyreoglobulin neg

CK7, S-100, actin+

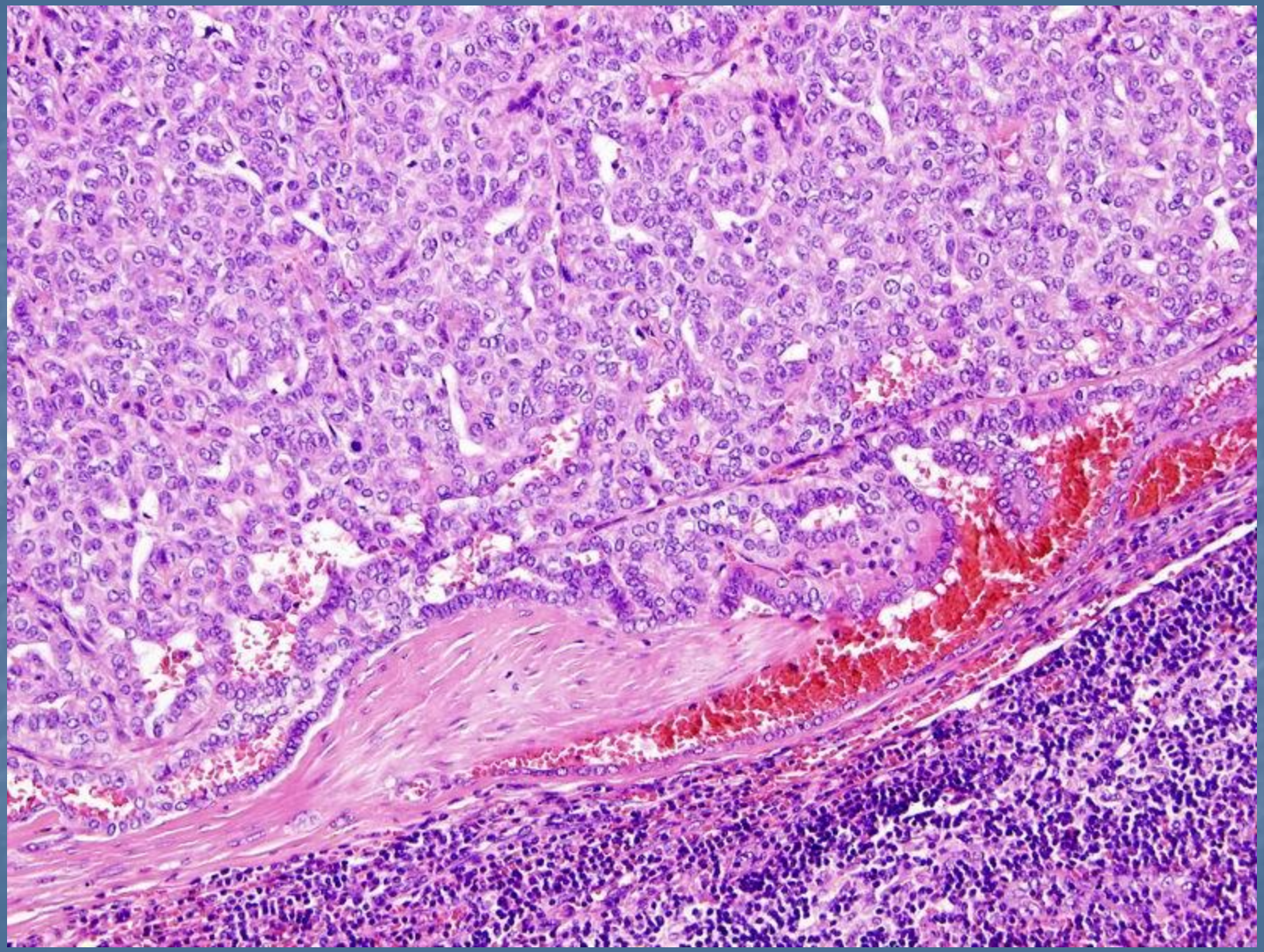
Papillary growth pattern, ground-glass nuclei



Infiltration of muscle of tongue, papillary and glomeruloid structures



Intact mucosa



neck lymph node metastasis at diagnosis in most cases of CATS

Differential diagnosis

- **PLGA polymorphous low grade adenocarcinoma**
  - Batsakis et al 1983, Freedman et al 1983
  - Evans, Batsakis 1984
- extensive nuclear ground-glass change in CAT and much wider range of morphological diversity in PLGA
- Clinical behaviour- LN meta in most cases

Differential diagnosis

- **Follicular and solid variant of papillary ca of thyroid**
  - Metastatic in cervical LN
  - Primary carcinoma of thyreoglossal duct
- Thyroglobulin and TTF1 negative
- Colloid is absent
- S-100 protein and myoepithelial markers positive

CAT is a distinctive entity

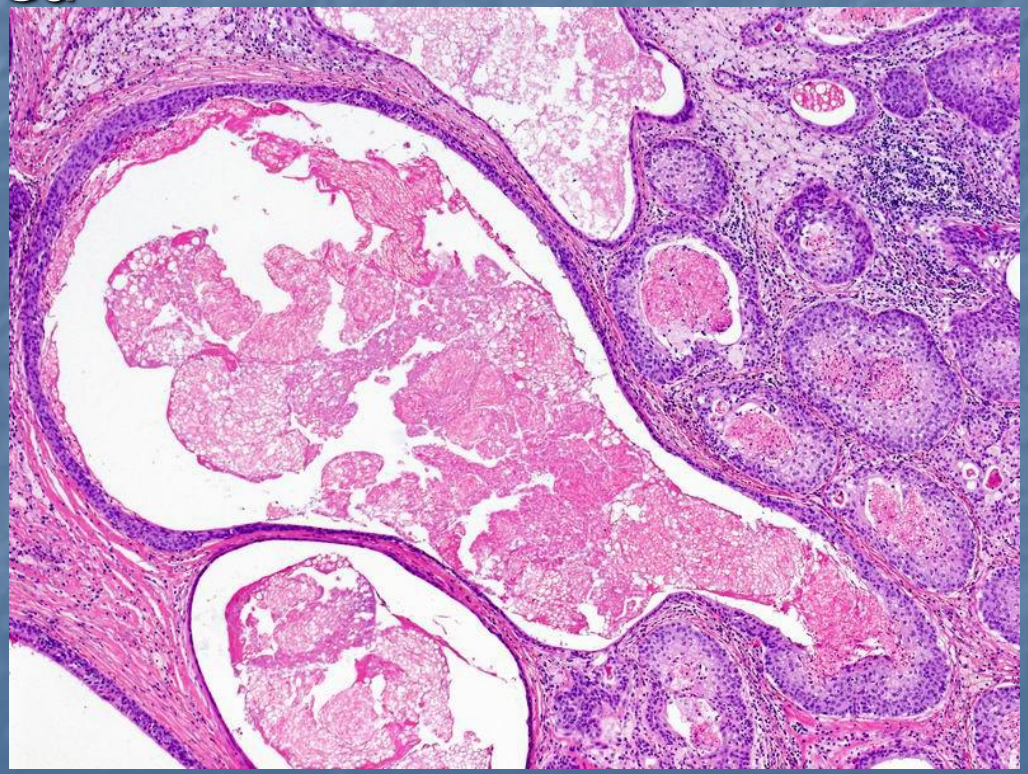
- Location in tongue, tonsils, palate
- Characteristic histology different from PLGA
- Clinical behaviour
  - neck lymph node metastasis at diagnosis
  - good prognosis, no tumor related death
  - Radiotherapy is currently of unproven benefit in PLGA, CAT seem to be radiosensitive

Keratocystoma

- very rare benign tumor with only three cases having been published
- parotid gland
- children or young

adults are affected

- No recurrences



Nagao et al. Mod Pathol 2002:15:1005-1010

Known entities with new findings

- Sclerosing mucoepidermoid carcinoma with eosinophilia
- Adenomas with additional stromal components
  - Lymphadenoma
  - Lipoadenoma
  - Adenofibroma

Sclerosing mucoepidermoid carcinoma with eosinophilia

- is uncommon tumor of thyroid gland that occurs in setting of sclerosing Hashimoto thyroiditis
- it has indolent clinical behaviour
- two morphologically similar tumors of major salivary glands have been reported

Urano et al. Pathol Res Pract 2002:198:305-310

Lymphadenoma

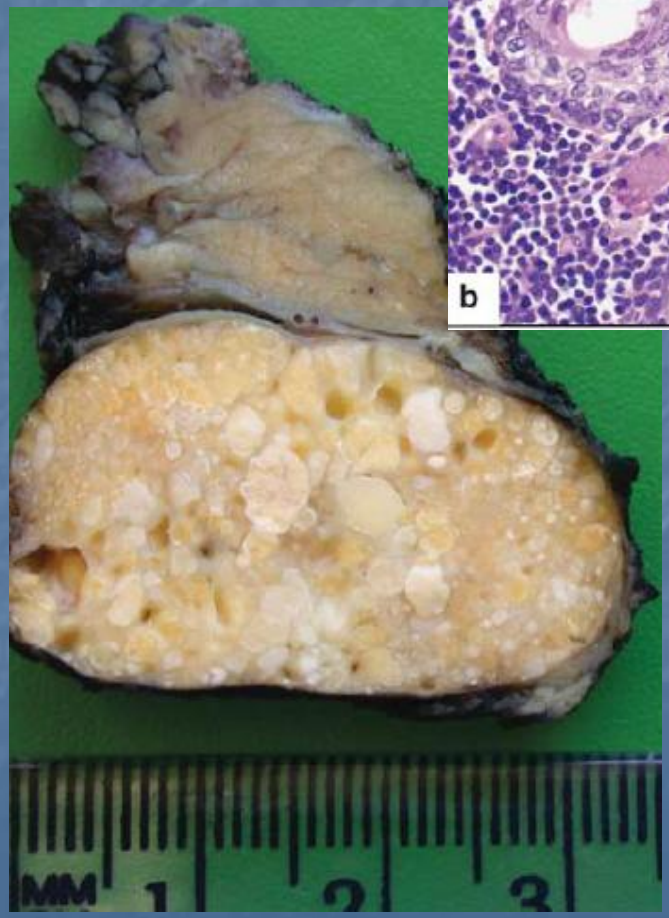
MODERN PATHOLOGY (2011), 1–10

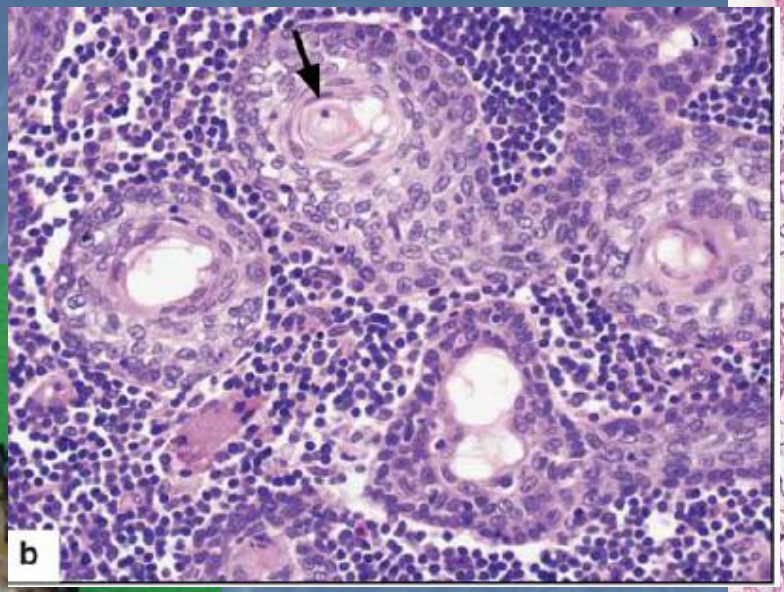
Lymphadenoma of the salivary gland: clinicopathological and immunohistochemical analysis of 33 tumors

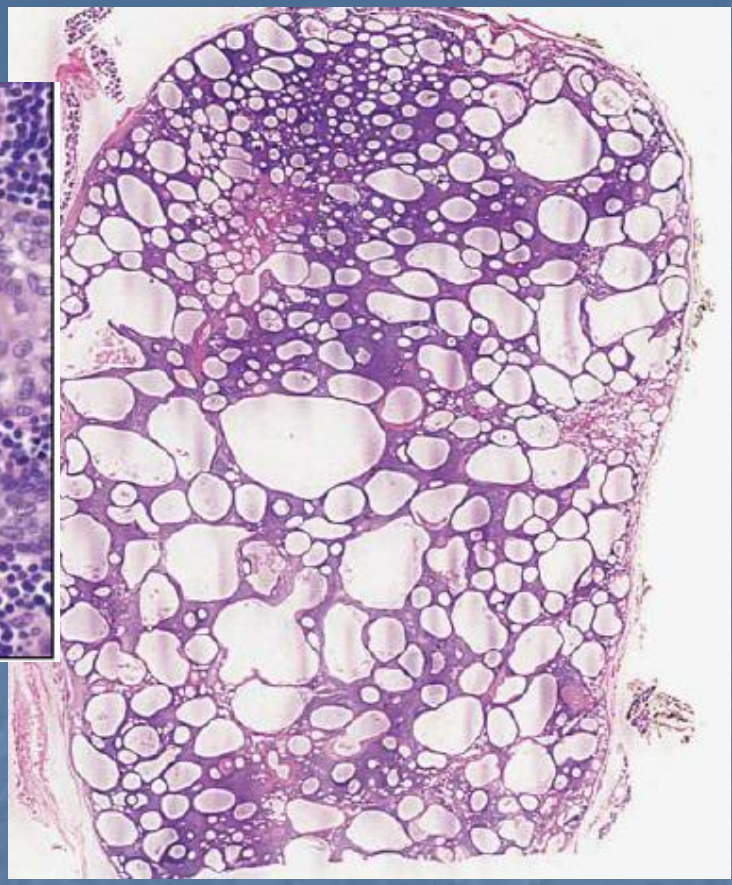
Raja R Seethala[1], Lester DR Thompson[2], Douglas R Gnepp[3], E Leon Barnes[1], Alena Skalova[4], Kathleen Montone[5], Shubhada Kane[6], James S Lewis Jr[7], Lynn W Solomon[8], Roderick HW Simpson[9], Ashraf Khan[10] and Manju L Prasad[11]

-lymphadenomas are rare salivary gland tumors
-their clinicopathologic characteristics and etiopathogenesis poorly understood
-most are located in parotid gland
-benign

Sebaceous lymphadenoma

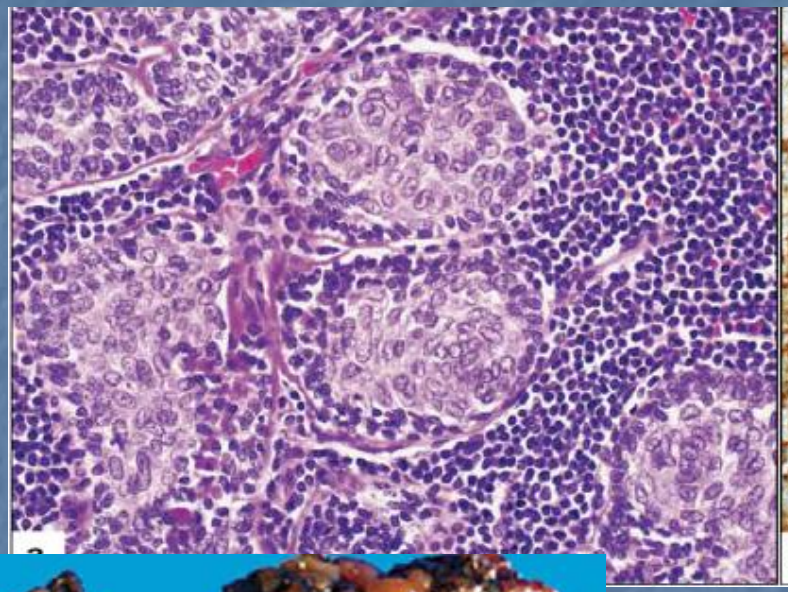


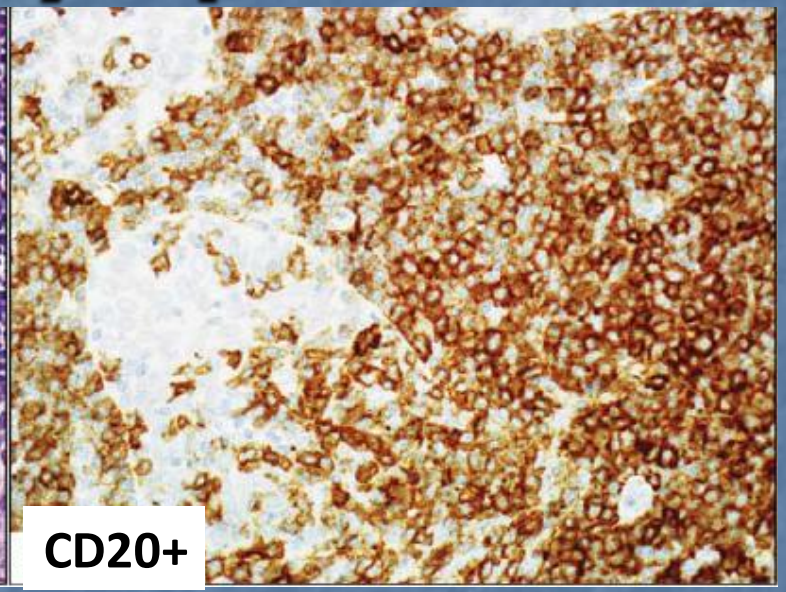




-tumors are well circumscribed, encapsulated
-cut surface is gray to yellow, solid to microcystic
-epithelial nests are solid, tubular or cystic

Non-sebaceous lymphadenoma





CD20+

-affect women and extraparotid sites more frequently than sebaceous tumors

Lipoadenoma (sialolipoma)

- Benign tumor consisting of adipose tissue admixed with variable amount of adenomatous glands
- Wide age range, more males
- Oncocytic, squamous and sebaceous differentiation common

Nagao et al. Histopathology 2001:38:30-36

Adenofibroma

- Very rare benign tumor characterized by admixture of adenomatous glands and fibrocellular stroma
- Metaplastic changes and cystic dilatation common


Thank you for attention
21nd National Congress of Pathology, İzmir, 16 -20 November 2011