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Adenomyoepitheliomas of the Breast Frequently Harbor Recurrent Hotspot Mutations in PIK3-AKT Pathway-related Genes and a Subset Show Genetic Similarity to Salivary Gland Epithelial-Myoepithelial Carcinoma

汇报人：许秀丽

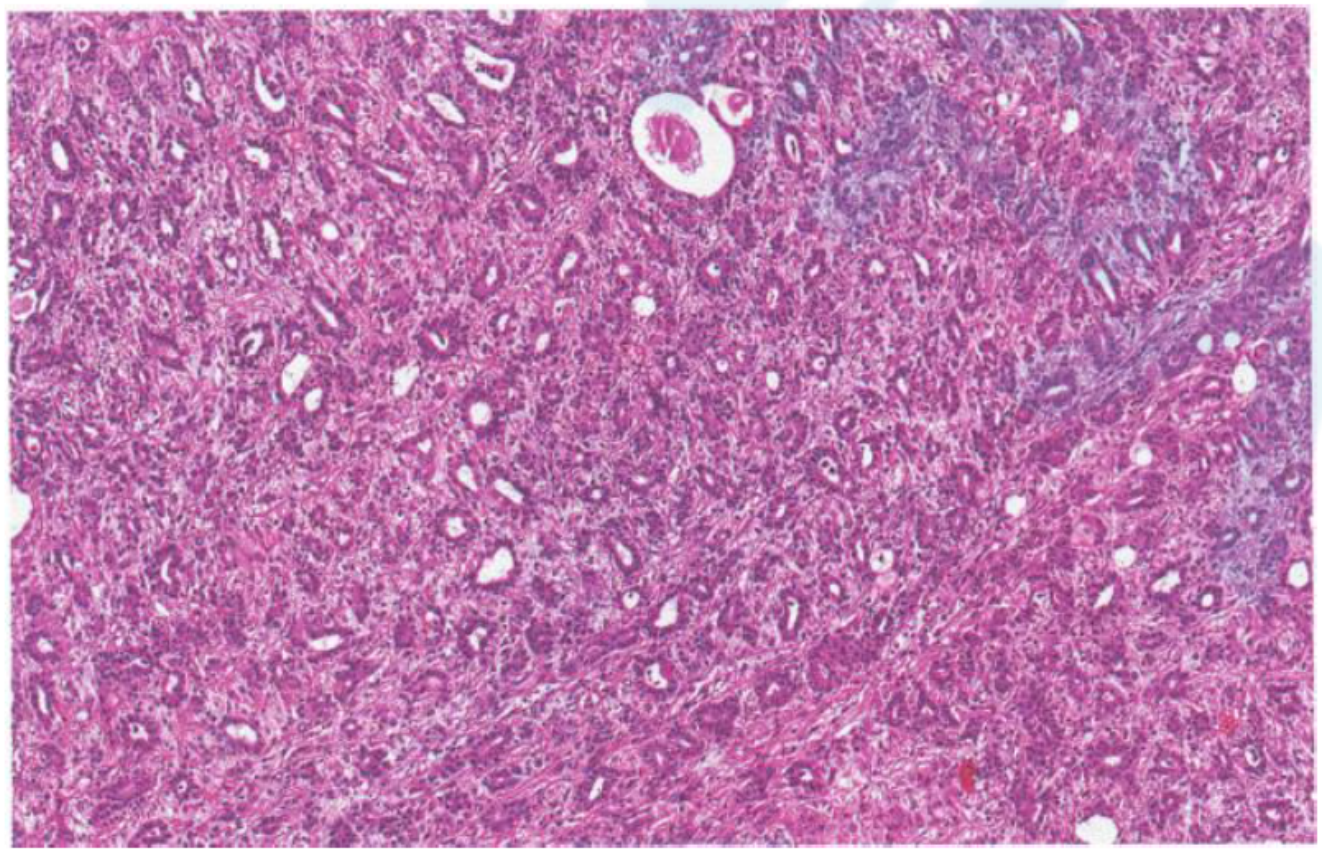
乳腺腺肌上皮瘤

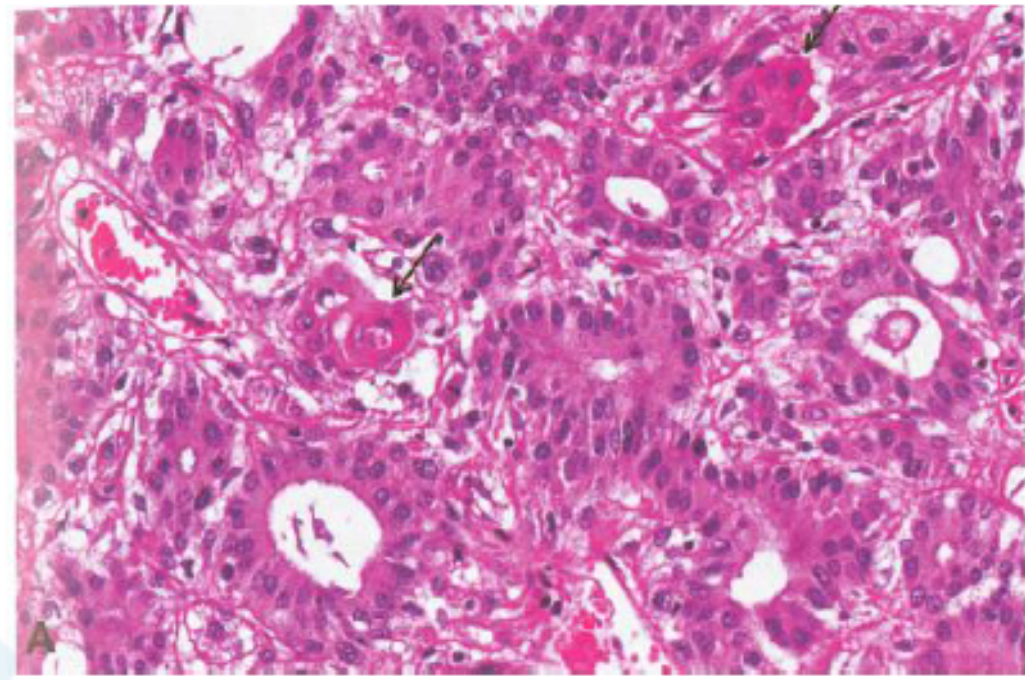
- **定义**：腺肌上皮瘤（Adenomyoepitheliomas，AME）是由肌上皮细胞围绕衬覆腺上皮的小腔隙增生而形成的肿瘤。罕见情况下，AME 的一种或两种成分可发生恶变（伴有癌的AME）。

- **临床特点**：AME 通常表现为乳腺中心部位的肿块，多为绝经后妇女。

- **大体检查**：AME 常为大于1cm 的圆形结节，中位大小2.5cm。伴有癌的AME 体积大，部分病例界限清楚，常见囊性变、坏死和钙化。

- **组织病理学**：AME 以被覆上皮的腔隙周围肌上皮细胞层增生为特点。结构上表现为分叶状、乳头状、小管状和混合性生长方式。肌上皮细胞可表现为多种形态，包括梭形、上皮样及富含糖原的透明细胞。腺体成分可出现大汗腺化生、鳞状上皮化生和皮脂腺分化。





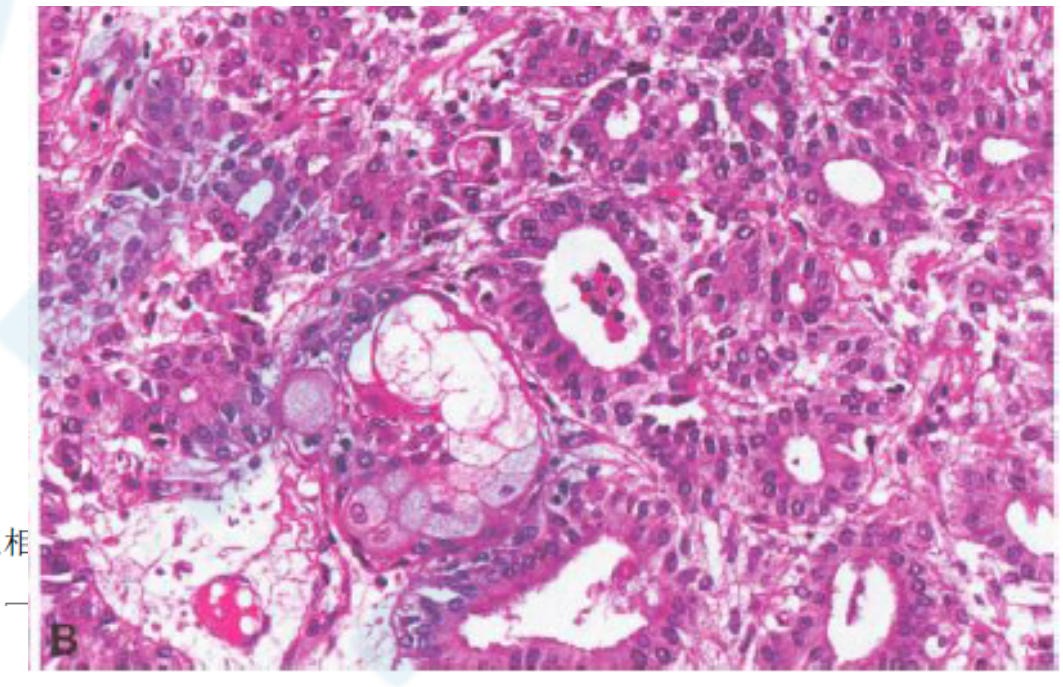


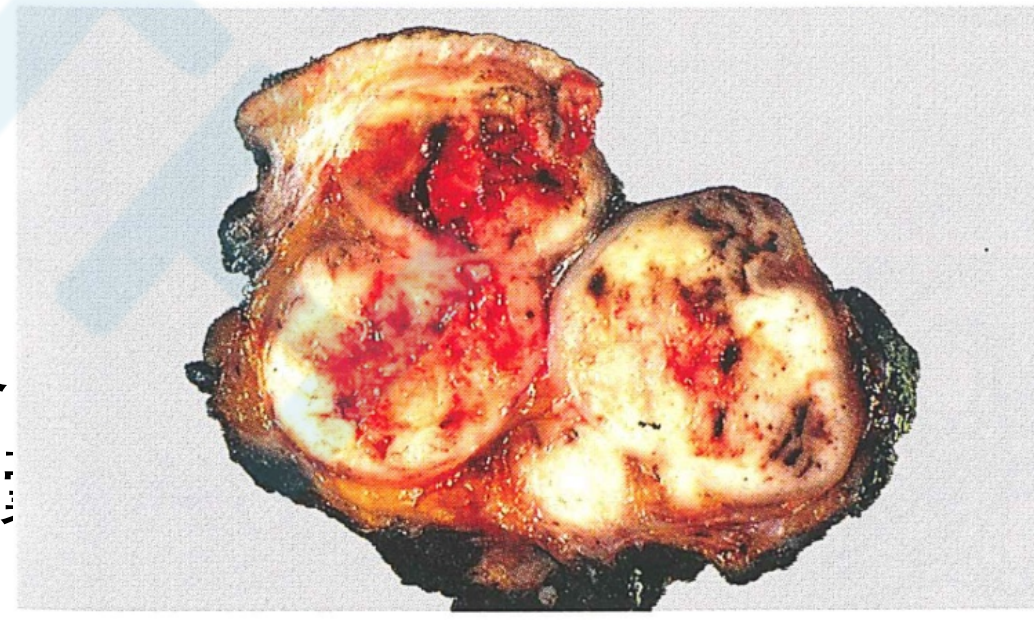
图 9.06 腺肌上皮瘤。被覆腺上皮细胞的小管及其周围环绕的明显的胞质透明肌上皮细胞形成双相生长方式。

上皮-肌上皮癌

Epithelial-myoepithelial carcinomas, EMC

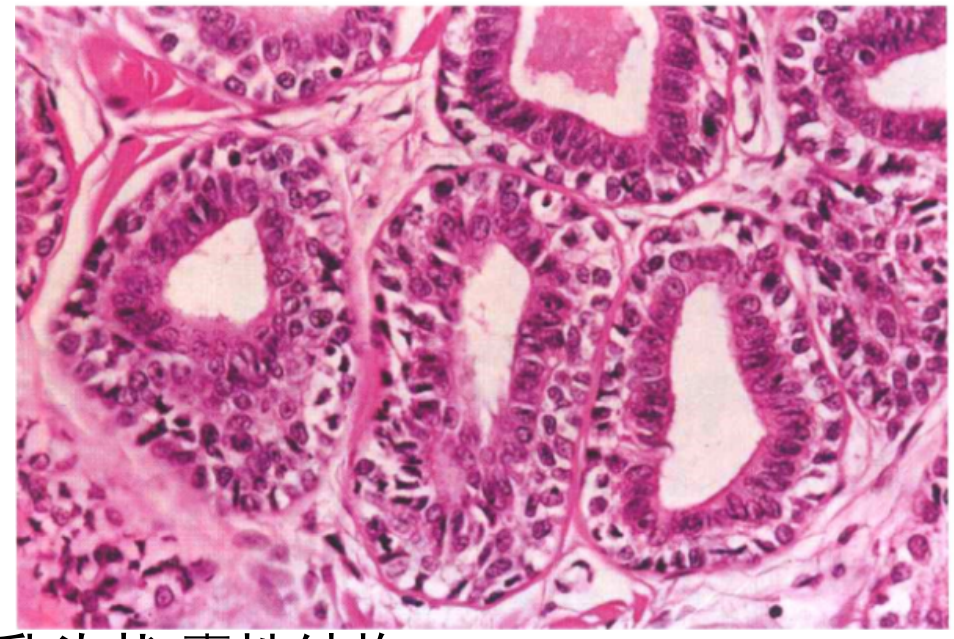
- **定义**
  - 一种发生于涎腺的恶性肿瘤，由内层的腺腔导管上皮与外层的肌上皮两种细胞组成
- **好发部位**

  大部分发生于腮腺、下颌下腺，少部分发生于鼻腔鼻窦、上腭
- **流行病学**
  - 少见的涎腺肿瘤，占涎腺恶性肿瘤＜5%
  - 好发于60-70岁女性
- **临床表现**：缓慢生长的无痛性包块
- **大体特征**
  - 多结节状，质韧，呈推挤式边界
  - 部分包膜，小部分（30%）出现



上皮-肌上皮癌
Epithelial-myoepithelial carcinomas, EMC

- **组织病理学**
  - 分叶状生长方式
  - 双层上皮
- **经典型EMC**
  - 内层---小的腺腔导管细胞，胞浆嗜酸性
  - 外层---多边形的肌上皮细胞，胞浆透亮
- **变异型EMC**
  - 出现筛状、基底细胞样排列，Verocay样生长，乳头状/囊性结构
  - 伴有皮脂腺分化、嗜酸细胞化生/顶浆分泌、双层细胞透明变、鳞化
  - 高级别转化、砂粒体



- **免疫组化**
  - 低分子量角蛋白在腺腔导管上皮高表达，肌上皮成分低表达
  - 肌上皮成分高表达肌上皮标记，如：SMA，HHF35，P63，calponin
- **预后**
  - 通常为低度恶性，局部复发率30-50%，淋巴结转移15-20%，远处转移罕见
  - 5年生存率80-94%，10年生存率72-90%
  - 预后因素包括肿瘤大小、边界情况、高级别转化、肌上皮间变、坏死、淋巴管侵犯

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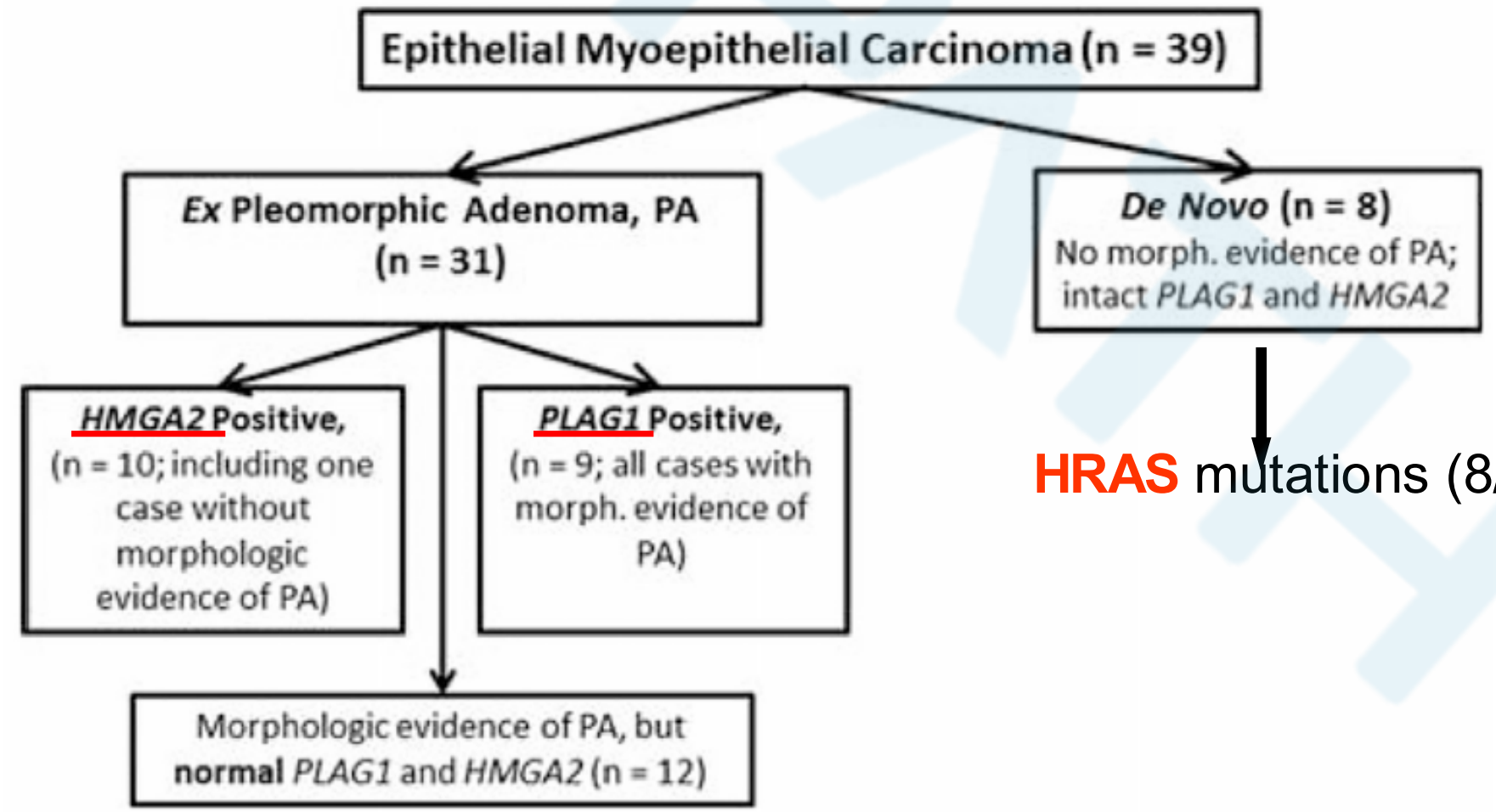
Epithelial-Myoepithelial Carcinoma:



HRAS mutations (8/23,35%).

MATERIALS AND METHODS

- 19 cases of breast-AME from 1990 to 2018；
- A tumor was referred to as “malignant AME” if the tumor exhibited overgrowth of epithelial or myoepithelial component, severe cytologic atypia, infiltrative growth pattern, increased mitotic activity (> 3/10 HPF) or necrosis.

- Immunohistochemistry

  estrogen receptor (ER)

- Fluorescence In Situ Hybridization

  PLAG1 and HMGA2 rearrangements

- Targeted Next-Generation Sequencing

RESULTS

TABLE 1. Clinical and Histologic Features of 19 Cases of Breast Adenomyoepitheliomas

Case#	Age (y)	Laterality	Size (cm)	Category (Benign/ Malignant)	Follow-up (mo)	Recurrence	Dominant Architecture	Myoepithelial Cells	Mitosis	Cytologic Atypia	Necrosis	Metaplasia/ Associated Findings	ER Expression
1	83	L	0.8	Benign			Tubular	Clear	1/10 HPF	Mild			Pos
2	47	R	1.2	Benign	107	No	Tubular	Clear	0/10	Mild		Mucinous	Pos
3													os
4													os
5													eg
6													eg
7													os
8													os
9													os
10													os
11													os
12													os
13													os
14	43	R	0.6	Benign			Papillary	Clear, epithelioid	0/10 HPF	Mild			Pos
15	72	R	0.9	Benign	104	No	Spindle	Spindled	0/10 HPF	Mild			Pos
16	78	R	1.6	Malignant			Tubular	Clear	4/10 HPF	Severe			Neg
17	80	R	1.0	Benign	69	No	Tubular	Spindled, epithelioid	1/10 HPF	Moderate		Squamous	Pos
18	67	L	0.8	Benign			Papillary	Epithelioid	0/10 HPF	Mild		Collagenous spherulosis	Pos
19	65	R	1.0	Malignant (metaplastic carcinoma)	12	Chest wall, rib	Spindle	Spindled	10/10 HPF	Severe			Neg

- All patients were female with a median age of 65 years (range, 33 to 83 y).
- The tumor size varied from 0.6 to 2.5 cm.
- Of the 19 cases selected, 12 were classified as benign, and 7 malignant.
- All 12 benign cases were ER positive, whereas 4 of 7 malignant cases were ER negative.
- Adequate follow-up was available for 8 patients with a median of 52 months (range, 8 to 107 mo).

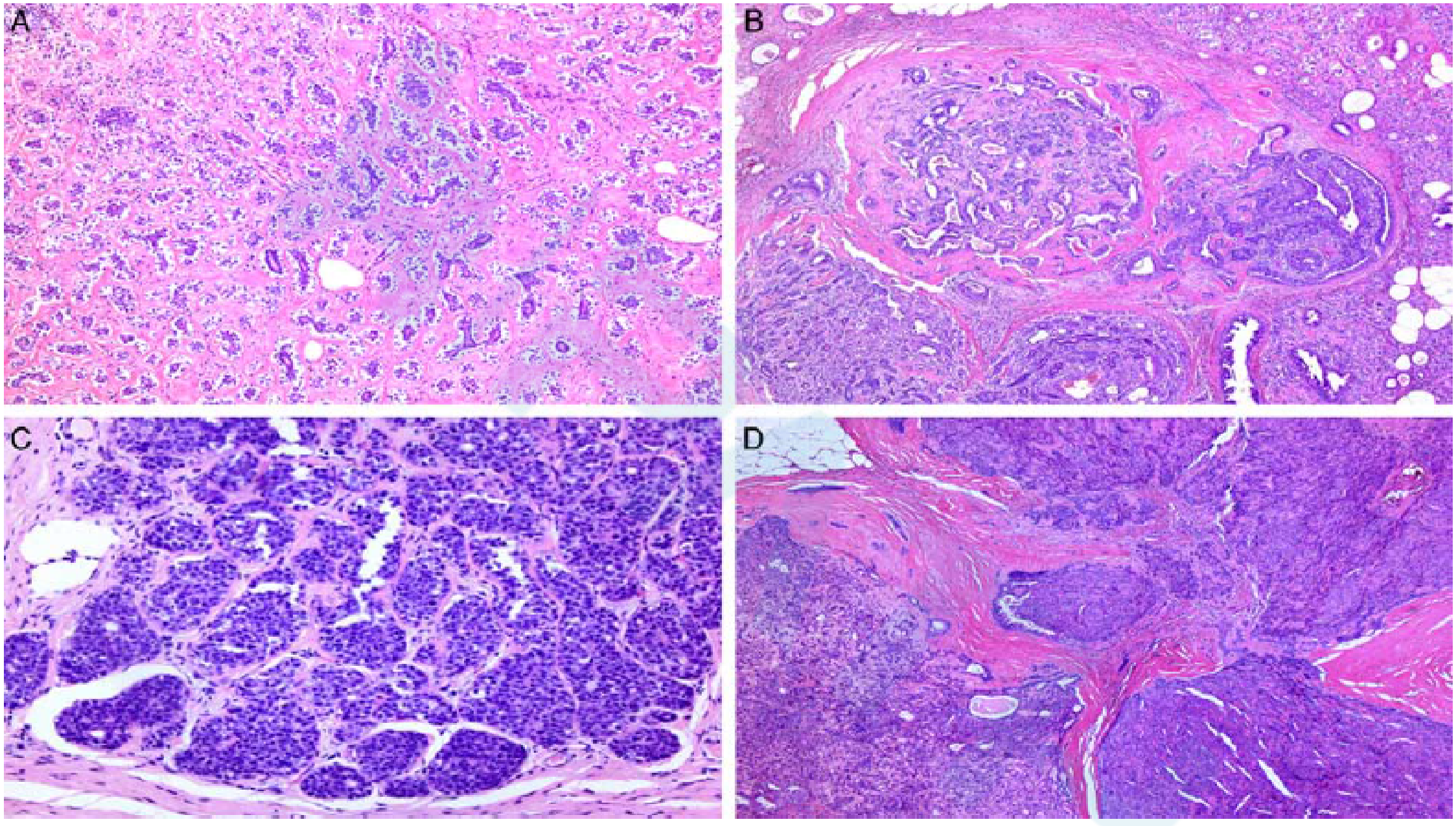


FIGURE 1. Adenomyoepitheliomas with dominant tubular (A), papillary (B), lobulated (C—solid nested proliferation of myoepithelial cells obliterating the glandular luminal component) and spindle (D) architectural patterns.

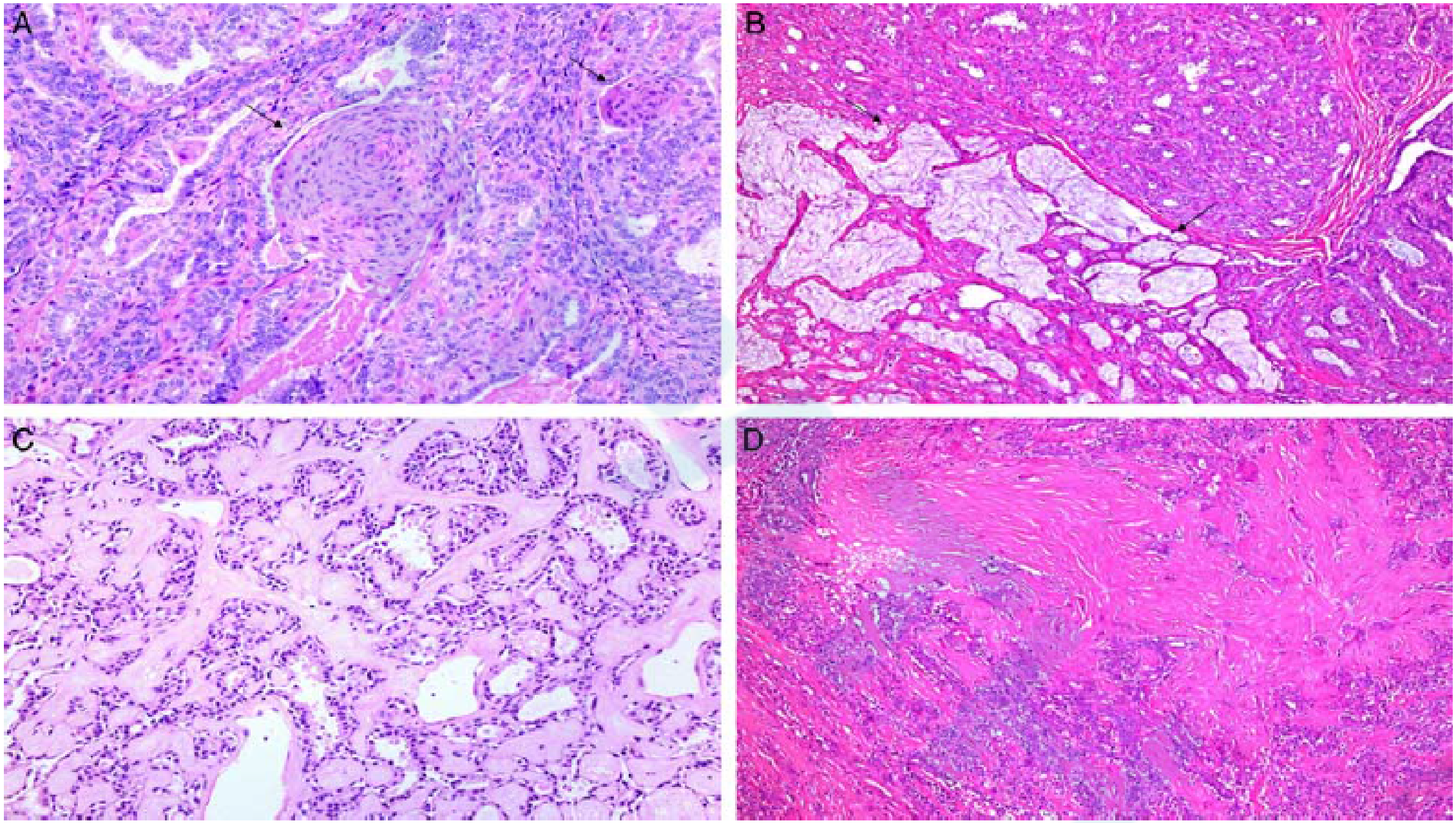


FIGURE 2. A case of adenomyoepithelioma (A) showing extensive squamous metaplasia (arrow); another case with mucinous metaplasia (B); a case with associated collageneous spherulosis (C), note the pink basement membrane like material encircled by myoepithelial cells; a case with prominent hyalinized stroma (D).

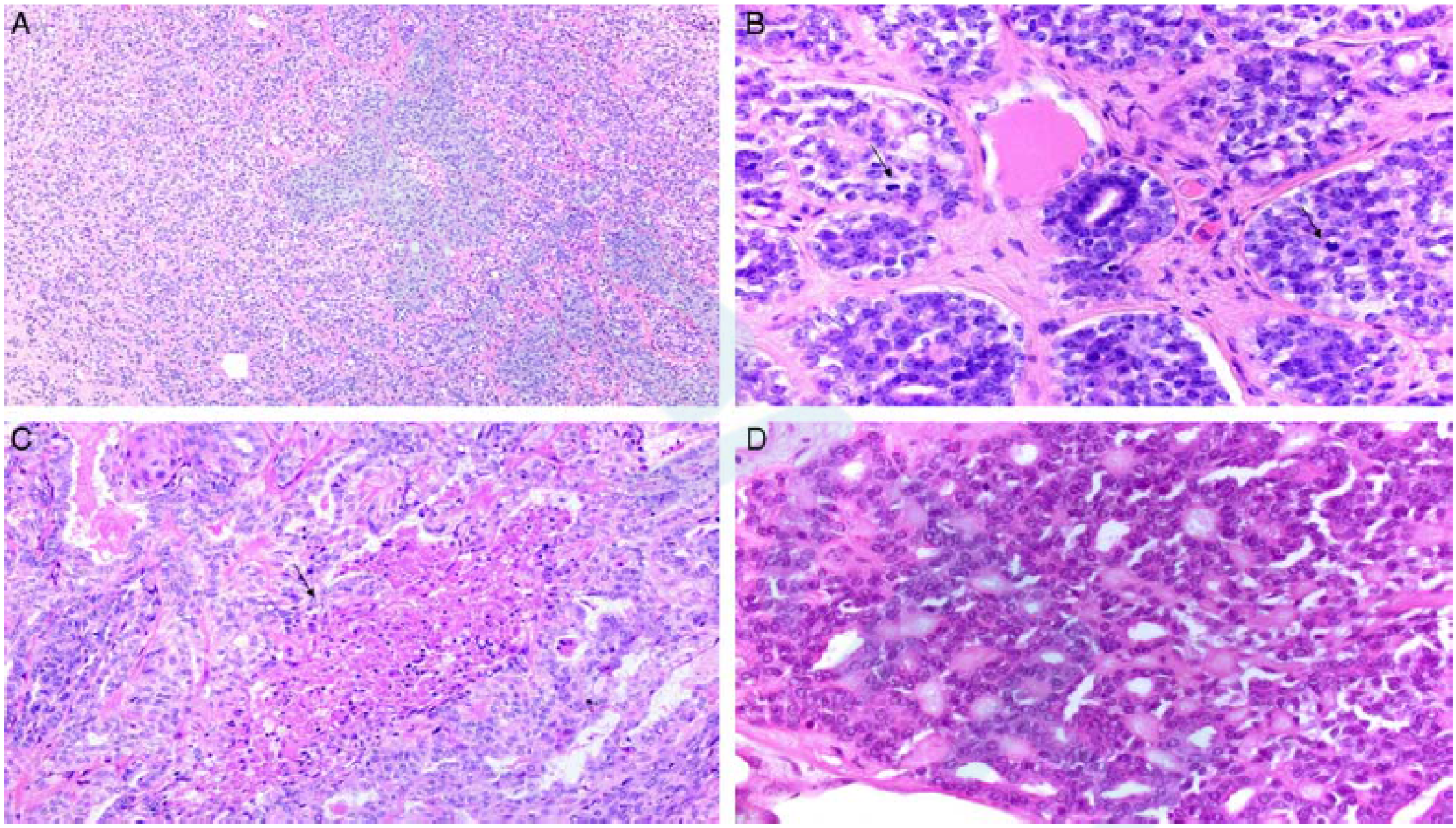


FIGURE 3. Malignant transformation in adenomyoepithelioma—a case with overgrowth of myoepithelial component (A); clear myoepithelial cells show severe cytologic atypia with vesicular nuclei, prominent eosinophilic nucleoli and increased mitotic activity (arrows-mitotic figure) (B); a case with areas of necrosis (arrow-mitotic figure) (C); a case with associated adenoid cystic carcinoma (D), note the basaloid cells encircling the basement membrane like material.

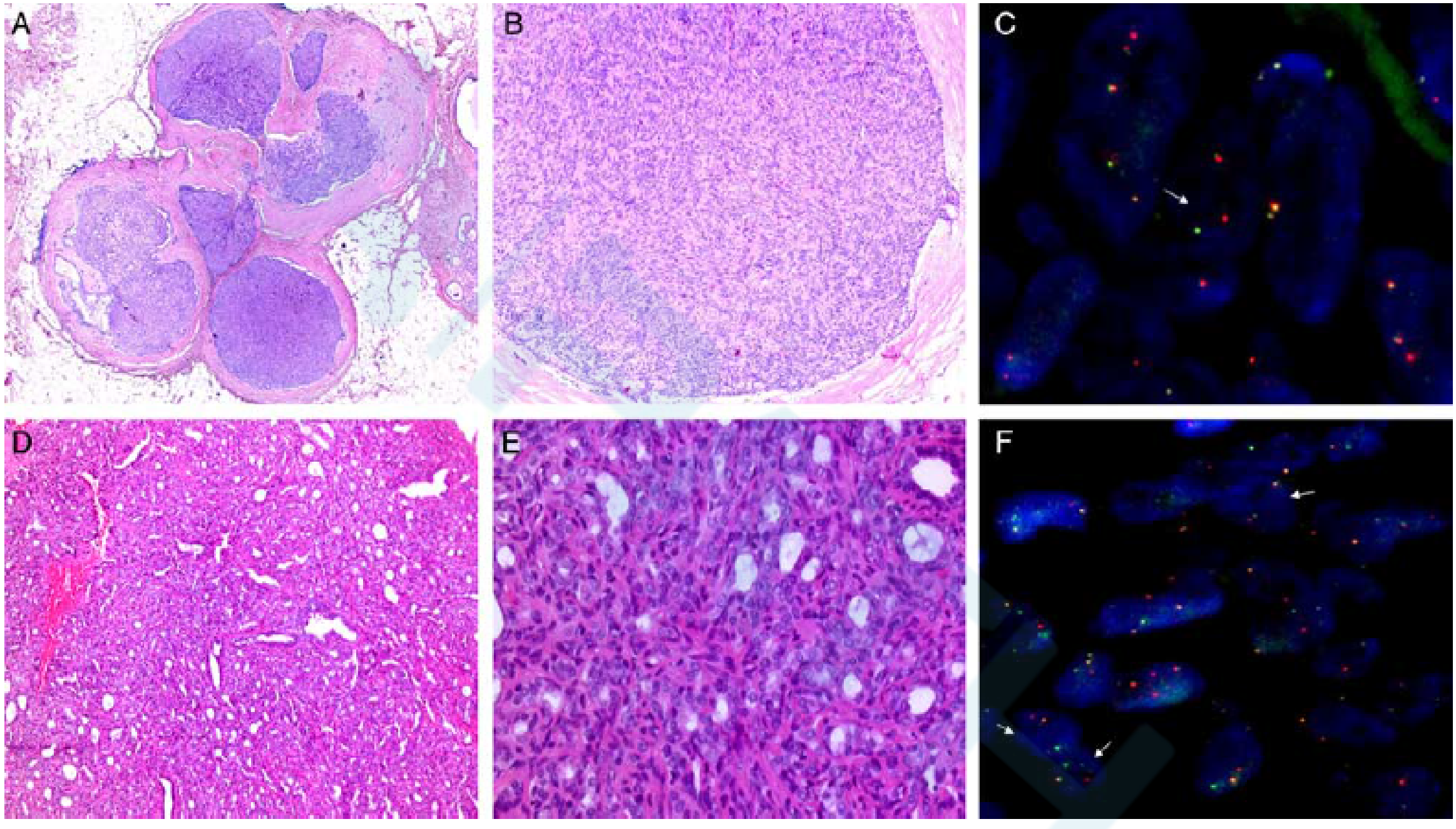


FIGURE 4. Case #13 with dominant spindle pattern, showing *HMGA2* gene rearrangement on FISH with corresponding hematoxylin and eosin–stained sections, low (A) and higher magnification (B). Note the cells (arrow) with orange and green break apart signals (C). Case #15 with hematoxylin and eosin–stained sections, low (D) and higher magnification (E) and corresponding *HMGA2* FISH showing break apart signals (F).

		Benign AME												Malignant AME						
		1	2	3	8	10	11	12	13	14	15	17	18	4	5	6	7	9	16	19
		ER+	ER+	ER+	ER+	ER+	ER+	ER+	ER+	ER+	ER+	ER+	ER+	ER+	ER-	ER-	ER+	ER+	ER-	ER-
Next Generation Sequencing	AKT1 p.E17K	35%			11%			42%						21%	43%					
	PIK3CA p.H1047R		31%	29%		26%	23%											43%		21%
	PIK3CA p.H1065L																			21%
	PIK3CA p.E542K					7%														
	HRAS p.Q61K																			39%
	APC p.P870S															49%				
	APC p.A1564P															10%				
	APC p.E1317Q																48%			
	ATM p.V410A	52%																		
	ATM p.F858L														47%					
	ATM p.P604S				50%															
	STK11 p.F354L								49%											
	EGFR p.E237K	51%																		
	FGFR3 p.F386L							44%												
	GNAS p.R187H	39%																		
	IDH2 p.W34X						7%													
	IDH2 p.V95I						6%													
	NOTCH1 p.T1573M						5%													
	RET p.R635C						6%													
	SMO p.R629K						7%													
FISH	PLAG1																			
	HMGA2								Breakapart		Breakapart									

Legend

Estrogen receptor status	
	ER positive
	ER negative
Mutation type	
	Missense mutation
	Nonsense mutation
	Failed extraction/FISH

FIGURE 5. The allelic frequencies of individual mutations and the relationship between the mutation type, histologic grading, FISH positivity, and ER positivity.

DISCUSSION

- Taken together, these results suggest that PIK3CA and AKT1 mutations function as driver mutations for a major subset of AME, and HRAS mutation is possibly instrumental in acquisition of an ER negative aggressive phenotype.

- Noteworthy is the finding that APC mutations were seen in 2 cases without PIK3CA or AKT1 mutations, and both the cases were malignant AMEs. Somatic mutations of APC have been reported in up to 18% of breast cancer patients.

- Our finding of HMGA2 rearrangements in a small subset (13%) of AMEs lends credence to a potential genotypicphenotypic relationship between AMEs and salivary gland EMCs, an idea further supported by the shared presence of HRAS mutations in both lesions.
- Our study, however, failed to detect PLAG1 alterations in AMEs, which on the contrary have been identified in a quarter of EMC cases.
- Similarly, we identified PIK3CA mutation in a large proportion of AMEs, which was reported to be rare in EMCs by El Hallani et al.

➢ Limitations：

a) Without adequate clinical follow-up, we are unable to determine whether the mutational status of our AME cases had any prognostic significance.

b) Our case series also suffered from having a limited number of ER-negative cases.

c) Also, without an evaluation of concurrent nonneoplastic tissue.

conclusion

- We confirmed that PIK3CA and AKT1 mutations are mutually exclusive and HRAS mutations co-occur with PIK3CA mutations in ER-negative AME displaying clinically aggressive behavior.

- We report the presence of HMGA2 alterations in 2 of 16 evaluable AME cases, supporting their relationship with EMC of salivary glands in at least a subset of cases.

- Our results suggest that PIK3CA, AKT1 and HRAS may serve as potential actionable targets in clinically aggressive AMEs.

谢谢！

涎腺肿瘤的高级别转化

- 又称为肿瘤“去分化”，是指高分化的低级别肿瘤失去了原有的形态特征，转化为高级别肿瘤，在肿瘤中可见到低级别和高级别病变区域毗邻，但又截然分界的状态
- 可发生高级别转化的肿瘤：腺样囊性癌，黏液表皮样癌，腺泡细胞癌，肌上皮癌，上皮-肌上皮癌，多形性（低度恶性）腺癌，透明细胞癌，（乳腺样）分泌性癌
- 高级别转化区域：完全失去了低级别病变的结构特征，完全由间变肿瘤细胞伴大片坏死构成，形态上类似“低分化癌”或“未分化癌”，同时部分或完全丧失了原有的免疫组化表型和基因表型

参考李智教授的课件