ORIGINAL ARTICLE

Microsecretory Adenocarcinoma

A Novel Salivary Gland Tumor Characterized by a Recurrent MEF2C-SS18 Fusion

Justin A. Bishop, MD.Am J Surg Pathol. Volume 43, Number 8, August 2019

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WHO Classification of Tumors of Salivary gland

Malignant tumours	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Acinic cell carcinoma	8550/3
Polymorphous adenocarcinoma	8525/3
Clear cell carcinoma	8310/3
Basal cell adenocarcinoma	8147/3
Intraductal carcinoma	8500/2
Adenocarcinoma, NOS	8140/3
Salivary duct carcinoma	8500/3
Myoepithelial carcinoma	8982/3
Epithelial–myoepithelial carcinoma	8562/3
Carcinoma ex pleomorphic adenoma	8941/3
Secretory carcinoma	8502/3*
Sebaceous adenocarcinoma	8410/3
Carcinosarcoma	8980/3
Poorly differentiated carcinoma	
Undifferentiated carcinoma	8020/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3
Lymphoepithelial carcinoma	8082/3
Squamous cell carcinoma	8070/3
Oncocytic carcinoma	8290/3
Uncertain malignant potential	
Sialoblastoma	8974/1
Benign tumours	
Pleomorphic adenoma	8940/0
Myoepithelioma	8982/0
Basal cell adenoma	8147/0
Warthin tumour	8561/0
Oncocytoma	8290/0
Lymphadenoma	8563/0*
Cystadenoma	8440/0
Sialadenoma papilliferum	8406/0
Ductal papillomas	8503/0
Sebaceous adenoma	8410/0
Canalicular adenoma and other ductal adenomas	8149/0
Non-neoplastic epithelial lesions	
Sclerosing polycystic adenosis	
Nodular oncocytic hyperplasia	
Lymphoepithelial sialadenitis	
Intercalated duct hyperplasia	
Benign soft tissue lesions	
Haemangioma	9120/0
Lipoma/sialolipoma	8850/0
Nodular fasciitis	8828/0
Haematolymphoid tumours	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (776A). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*These new codes were approved by the IARC/WHO Committee for ICD-O.

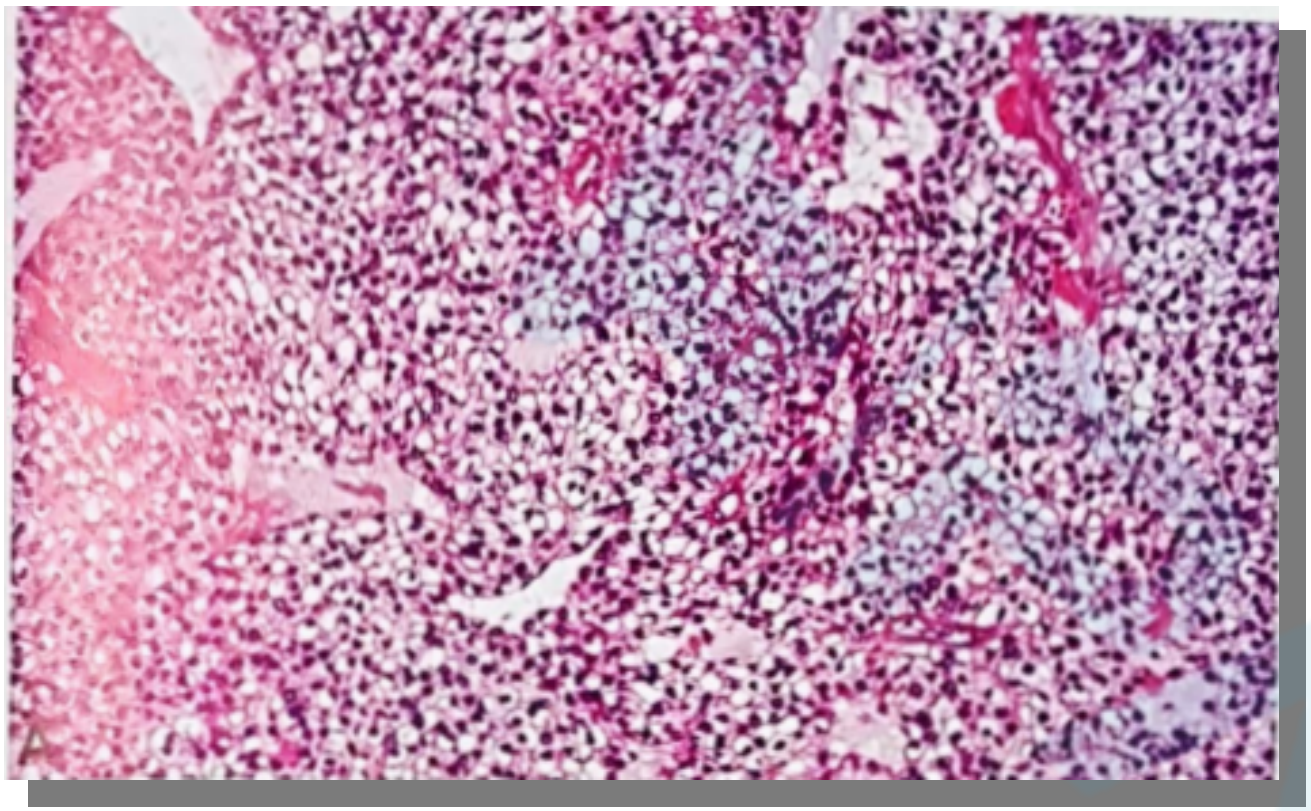
BACKGROUND

- clear cell carcinoma (mucoepidermoid carcinoma, adenocarcinoma NOS, or even squamous cell carcinoma):EWSR1-ATF1 fusion.

- “Warthin-like” or oncocytic variants of mucoepidermoid carcinoma:(Warthin tumors, oncocytomas, or oncocytic carcinomas) :MAML2 rearrangements

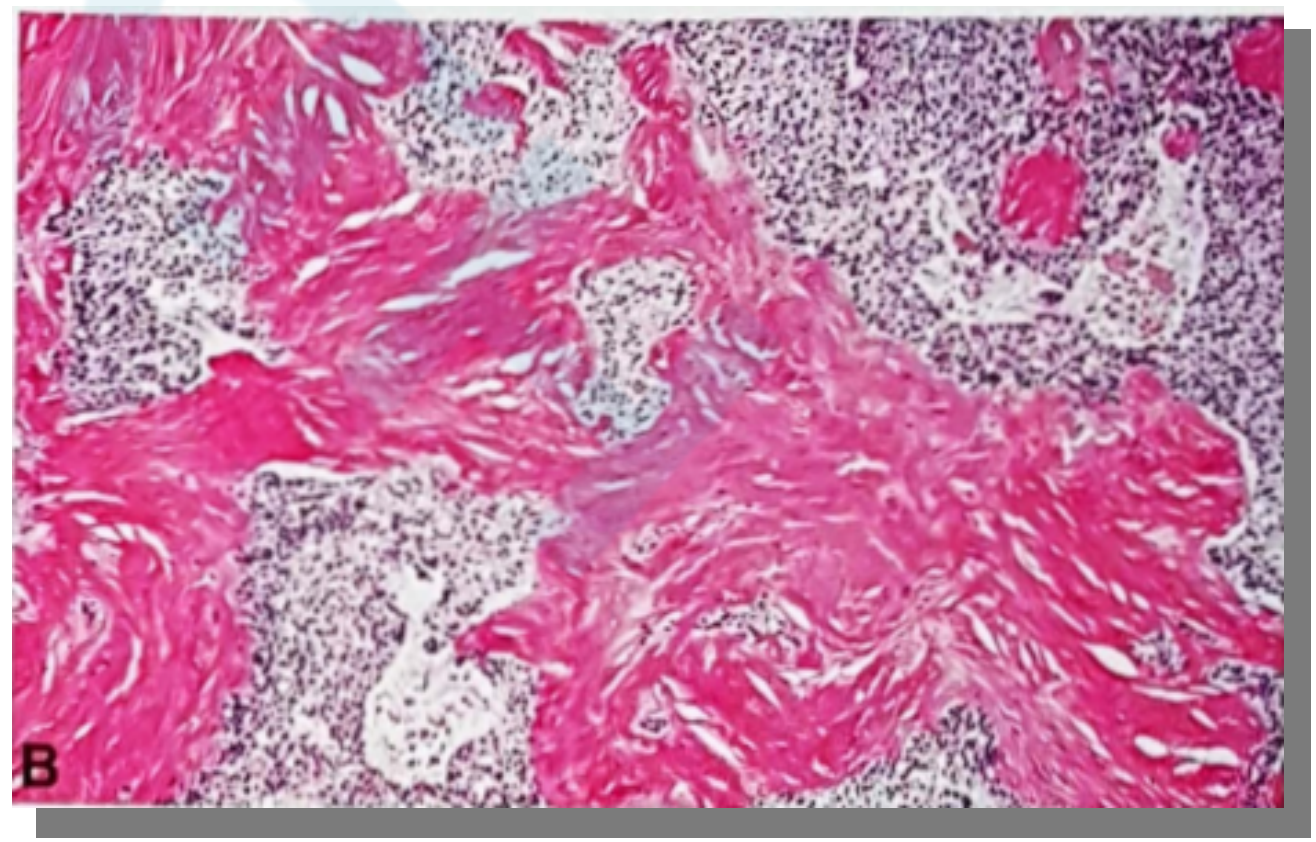
- secretory carcinoma (acinic cell carcinoma, adenocarcinoma NOS, mucoepidermoid carcinoma,), : ETV6 rearrangements

Clear Cell Carcinoma

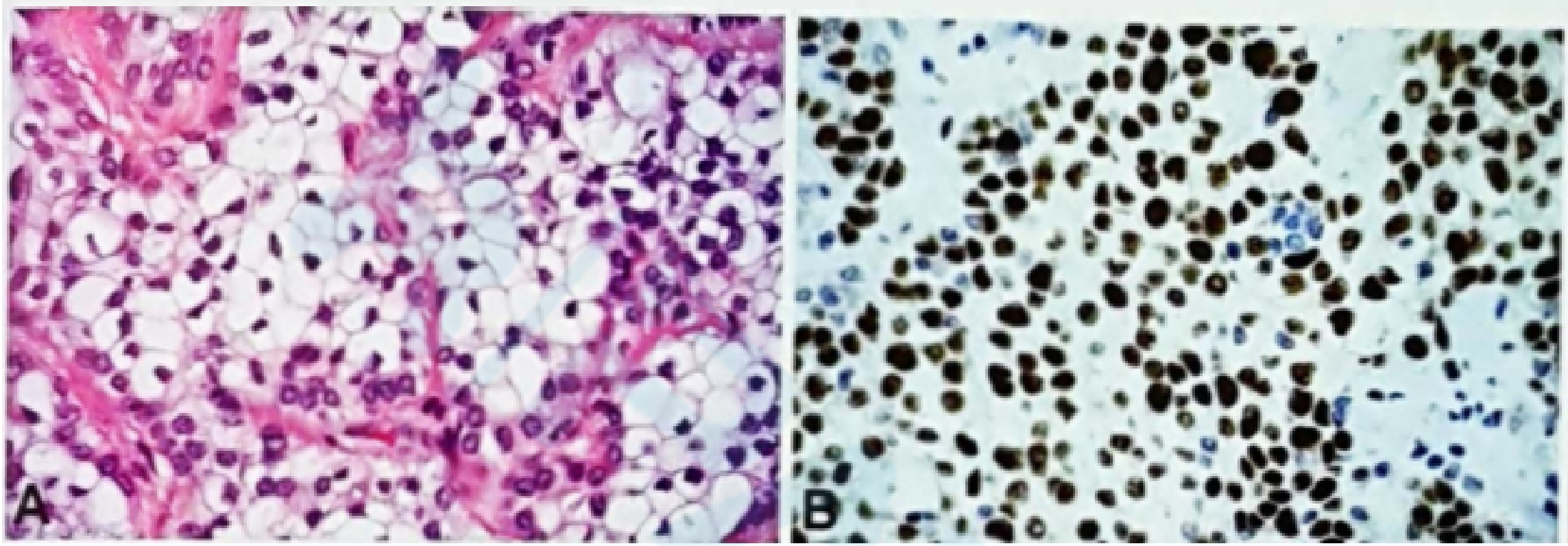


A Diffuse sheet-like growth, composed of neoplastic cells with clear cytoplasm.

B Tick bands of hyalinized (sclerotic) collagen intimately associated with clusters of neoplastic cells with clear cytoplasm.

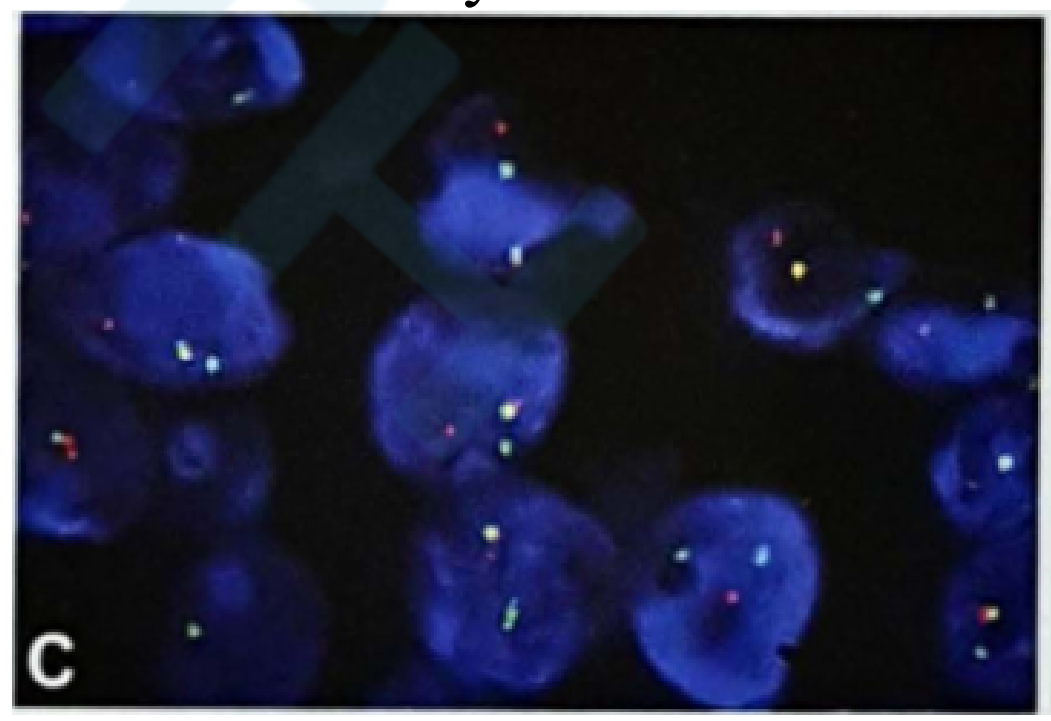


Clear Cell Carcinoma

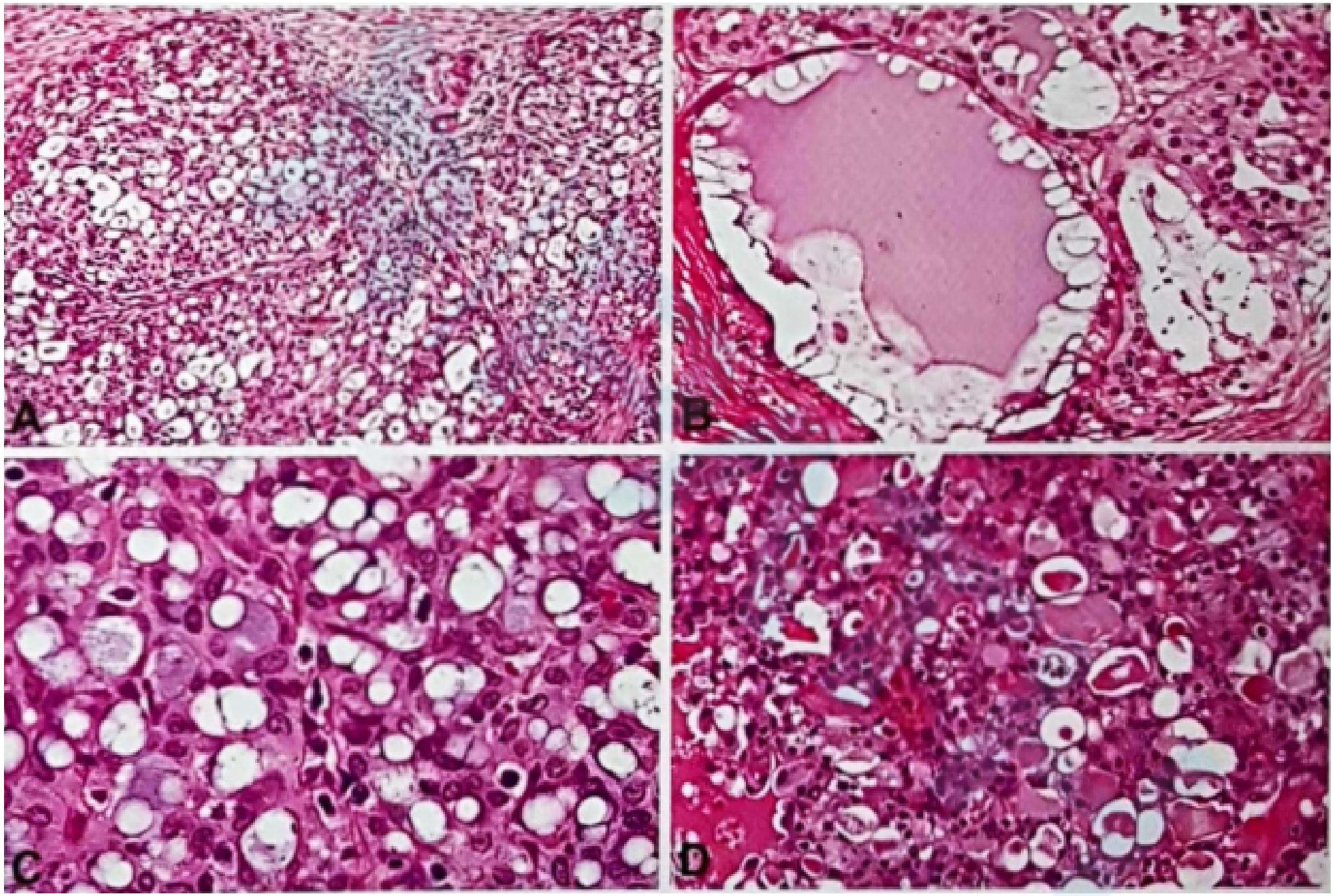


A Nests of neoplastic cells with clear cytoplasm: the nuclei are round to oval and centrally to eccentrically located. **B** CCCcells are consistently P63-reactive (diffuselly and strongly).

C EWSR1 break-apart FISH demonstrates several cells with split red and green signals, indicative of a translocation.

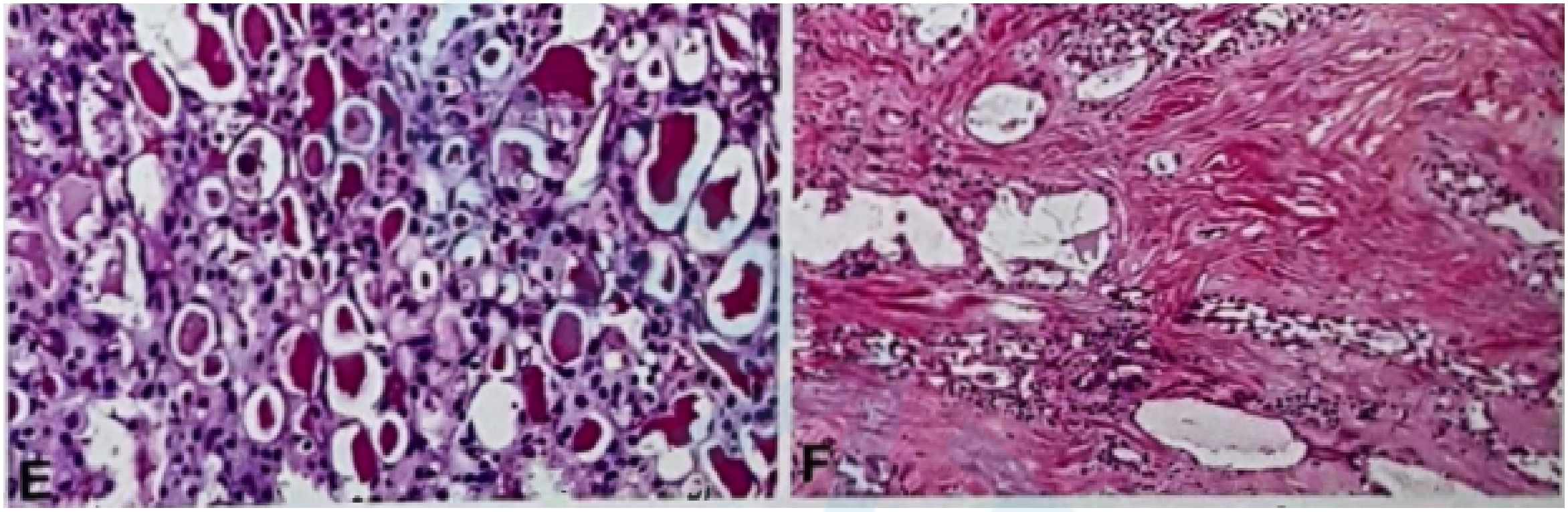


Secretory Carcinoma



A The tumor displays a lobulated growth patten with fibrous septa and is composed of microcystic/solid and tubular structures. **B** Macrocystic patten with abundant homogeneous secretion. **C** The tumour cells have bland vesicular round to oval nuclei, with finely granular chromatin and distinctive centrally located nucleolus. **D** Abundant eosinpphilic homogeneous secretions in microcystic and tubular spaces.

BACKGROUND



E Glandular secretion gives a positive acid-Schiff (PAS) reaction before and after enzyme digestion. **F** Trabecular neoplastic cellular structures embeded in a sclerotic stroma.

BACKGROUND

- Fusion-positive salivary gland carcinomas： bland, monotonous tumor nuclei.

- Not only has awareness of these fusions has aided in refining the histologic spectra of many already well-characterized tumors, but in the case of secretory carcinoma, the discovery of tumor-defining ETV6 fusions facilitated the recognition of an entirely novel salivary gland adenocarcinoma.

BACKGROUND

MEF2C (monocyte enhancer factor 2C)

location: 5q14.3
function: encoding a transcription factor in the MADS box transcription enhancer factor 2 (MEF2) family involved in normal muscle and nerve development.

Translocations involving MEF2C have been reported in a subset of acute lymphoblastic leukemia.

BACKGROUND

SS18 (SS18 subunit of BAF chromatin remodeling complex)

location: 18q11.2
function: encoding SSXT which is a member of the SWI/SNF chromatin remodeling complex.

Fusion of SS18 with one of the SSX genes is the well-established molecular hallmark of synovial sarcoma.

MATERIALS AND METHODS

- Cases

  ---5 cases (a near-identical, distinctive appearance) VS 23 cases (with variable histologic features，One of these control adenocarcinoma, NOS cases was “sclerosing microcystic adenocarcinoma.”)

- RNA Sequencing
- RT-PCR & Sanger sequencing
- Immunohistochemistry

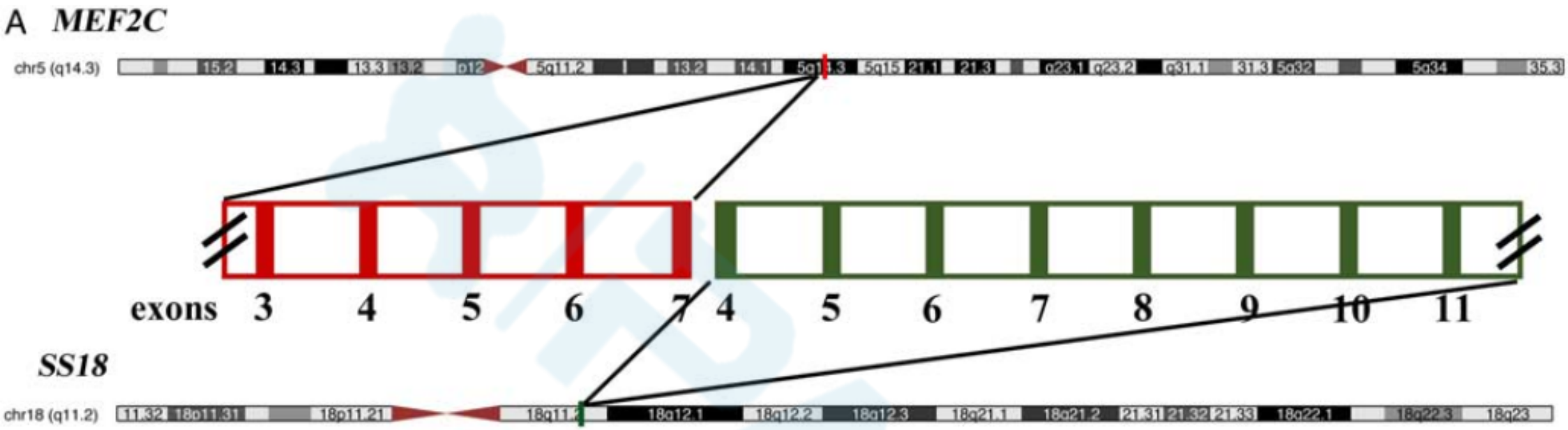
RESULTS

- RNA-Seq revealed that all 5 index adenocarcinomas harbored a unique MEF2C-SS18 fusion.

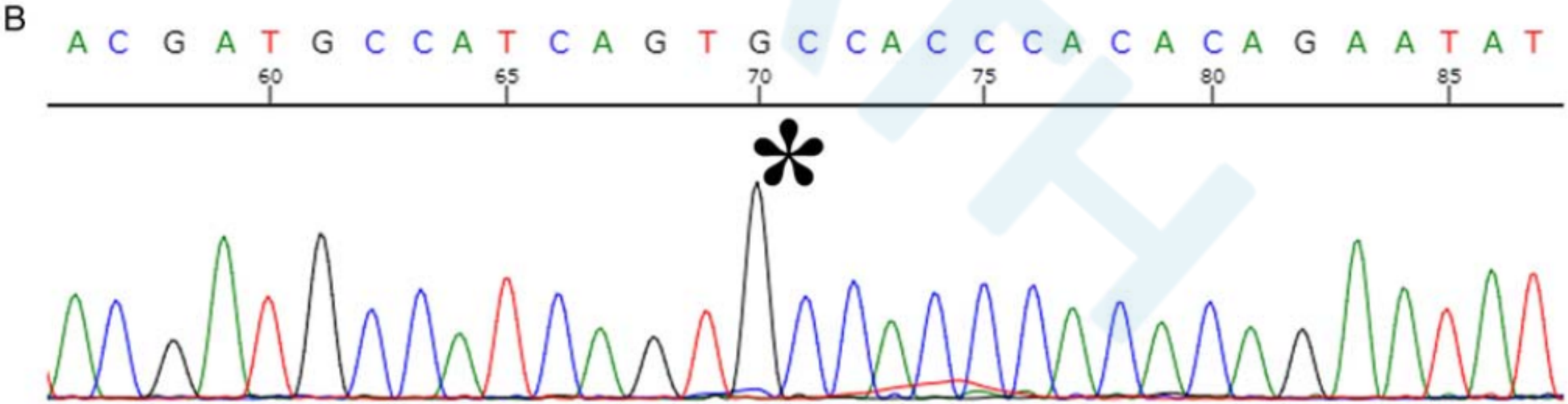
- All fusion break points involved exon 7 of the MEF2C gene and exon 4 of the SS18 gene.

- The fusion was independently confirmed by RT-PCR and Sanger sequencing in the 3 of the cases.

RESULTS



A, Diagrammatic representation of fusion product, which occurs between exon 7 of MEF2C and exon 4 of SS18.



B, Representative example of Sanger sequencing of RT-PCR product, which independently confirms the results of RNA-Seq. (asterisk "*" denotes breakpoint)

RESULTS

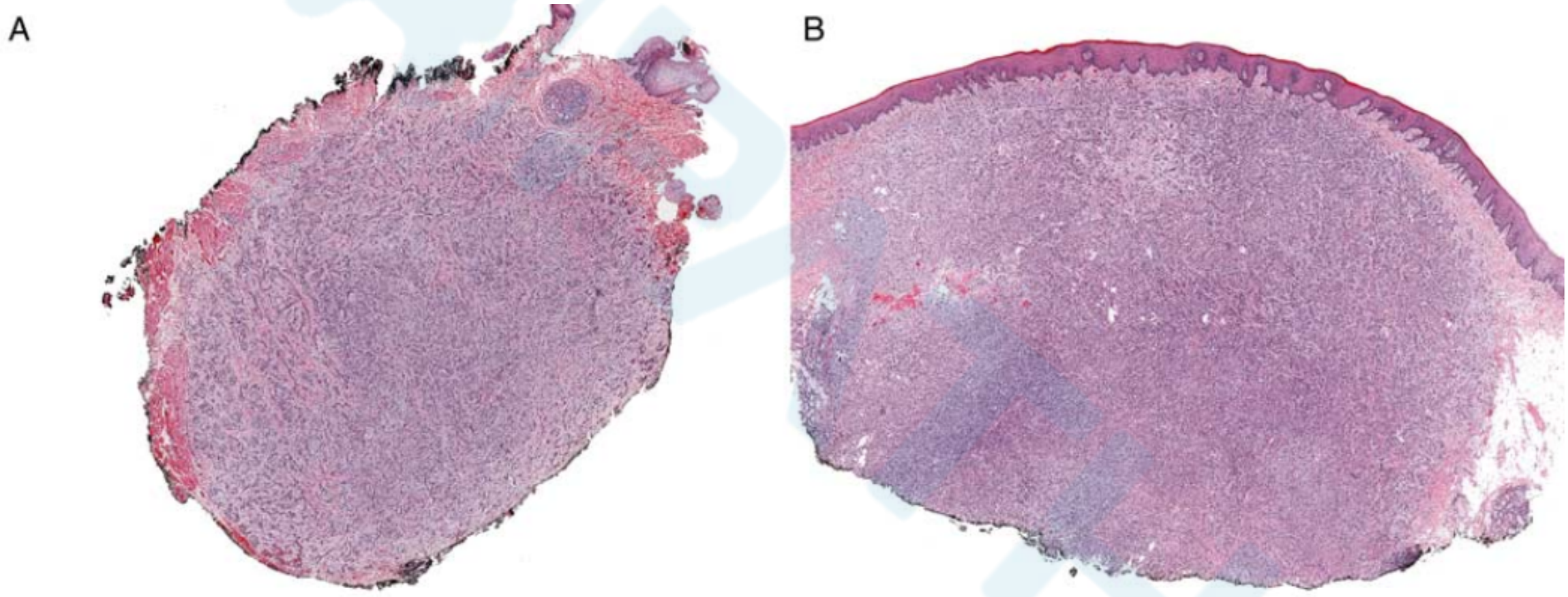
TABLE 1. Clinical and Demographic Findings of *MEF2C-SS18* Positive Microsecretory Adenocarcinoma

Case	Age (y)	Sex	Tumor Location	Oral Subsite	Presentation	Tumor Size (cm)
1	21	M	Oral cavity	Buccal	Painless mass	0.8
2	80	F	Oral cavity	Palate	Painless mass	0.8
3	48	F	Oral cavity	Buccal	Painless mass	2.2
4	32	M	Oral cavity	Palate	Painless mass	1.5
5	51	F	Parotid gland	NA	Painless mass	0.8

site　　oral cavity: 4（ buccal mucosa: 2; palate: 2）
　　parotid gland: 1
gender　　women: 3; men: 2
age　　21 to 80 years (mean, 46 y)
clinical symptom　　painless mass
tumor sizes　　0.8 to 2.2 cm (mean 1.2 cm).

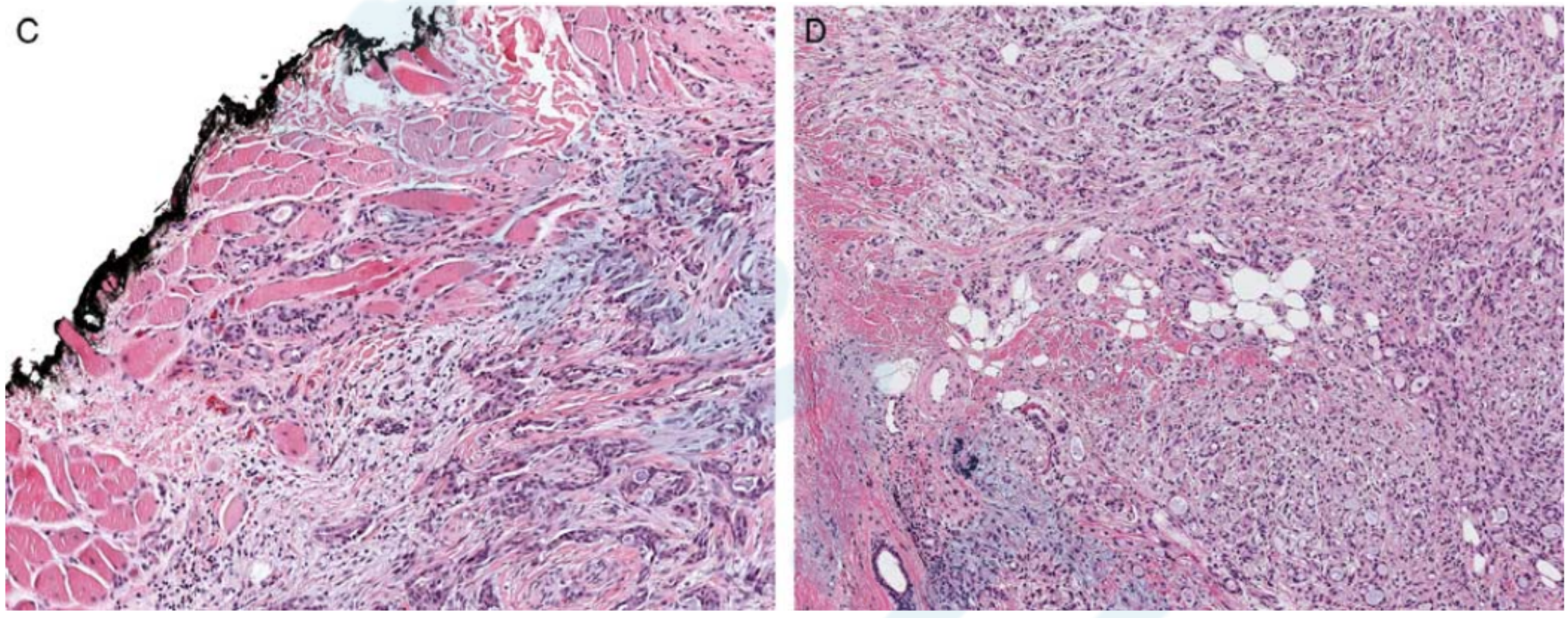
RESULTS

All 5 MEF2C-SS18-positive cases shared very similar histologic features.



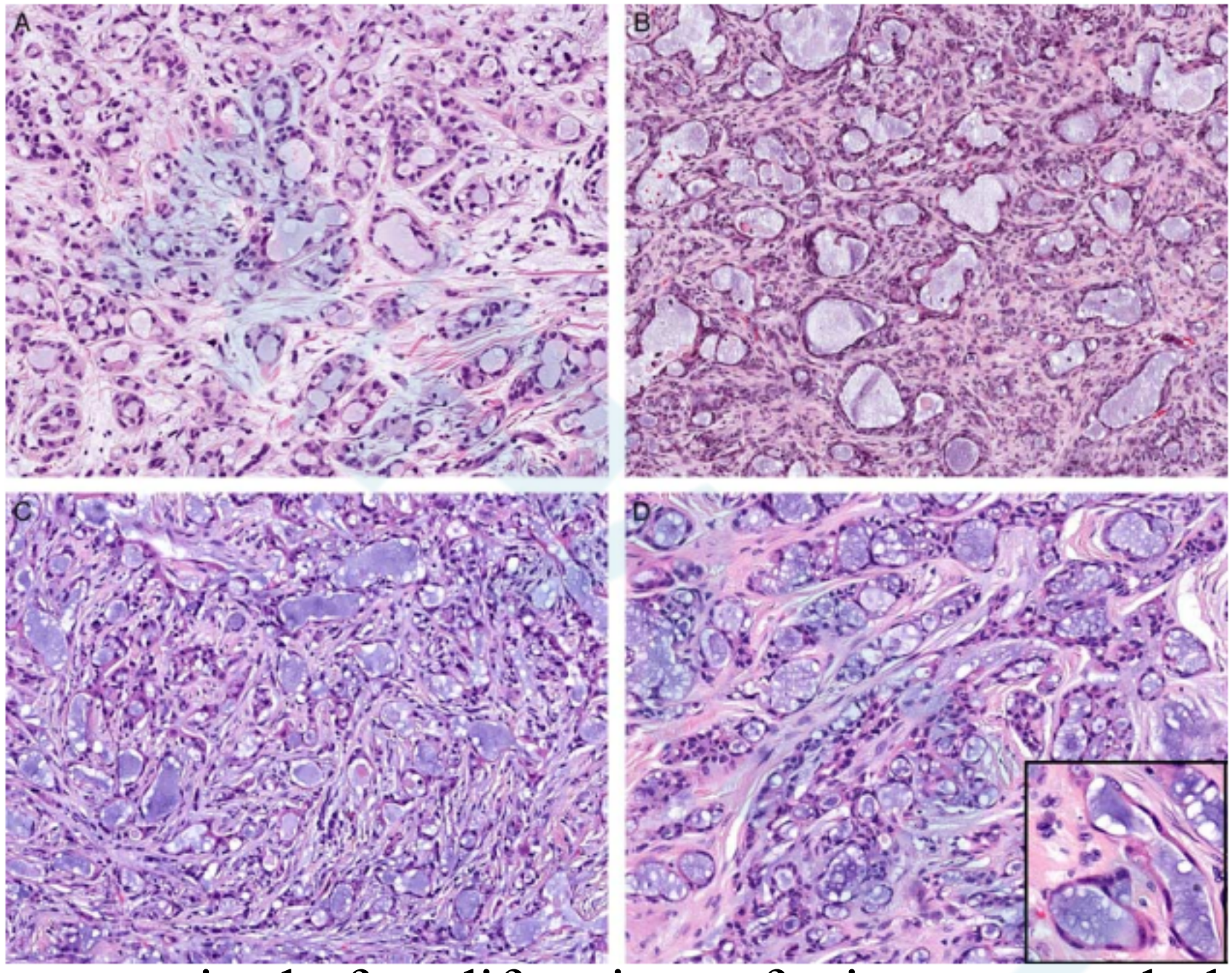
At low power, the microsecretory adenocarcinomas appeared to be relatively well circumscribed.

RESULTS



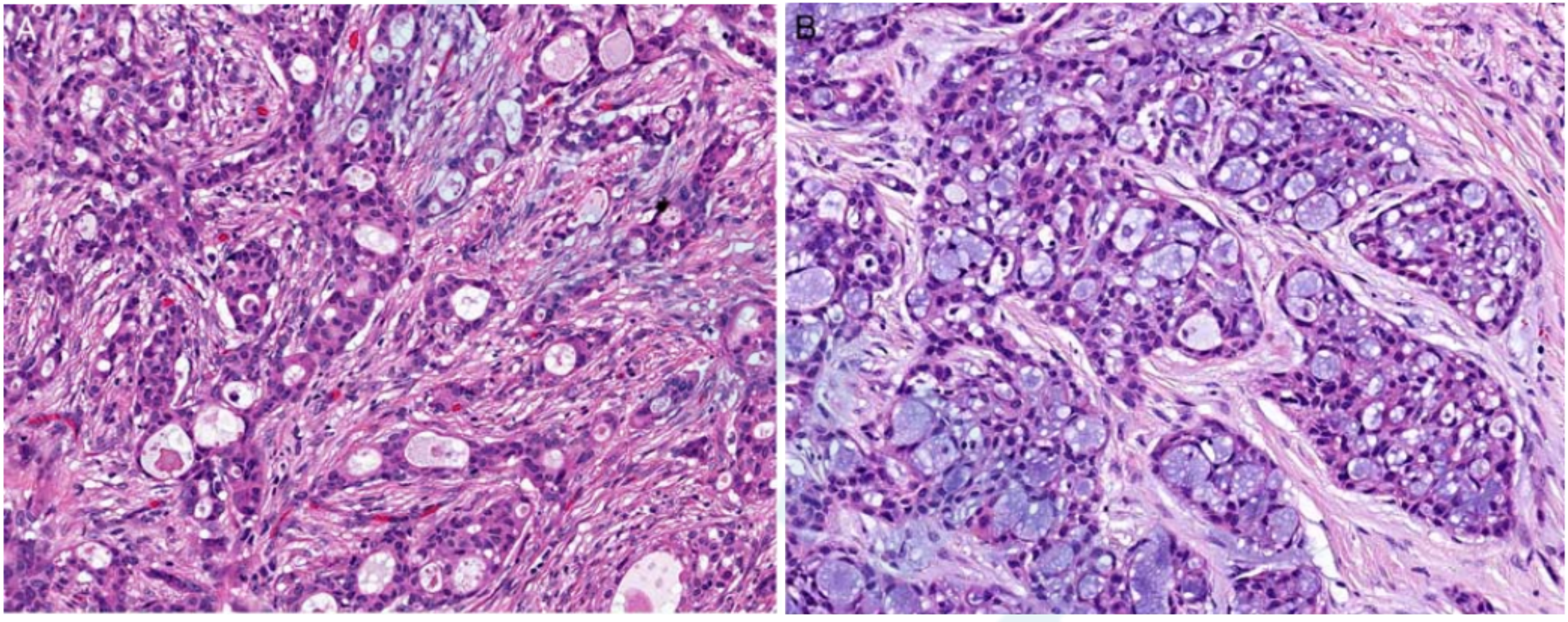
At high power an infiltrative border was apparent, with tumor invasion into skeletal muscle, collagen, and fat.

RESULTS



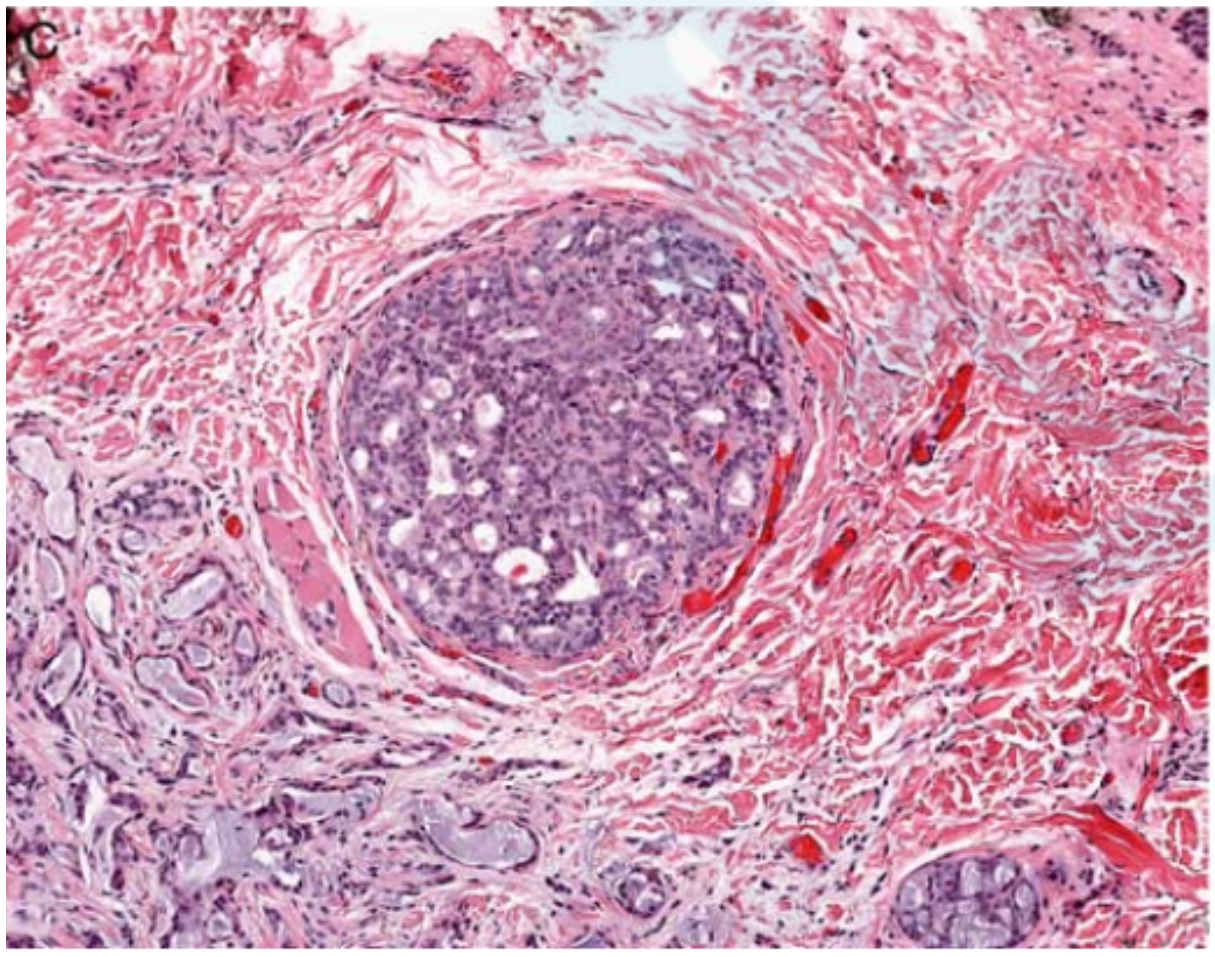
They were comprised of proliferations of microcysts, tubules, and cords lined by intercalated duct-like cells with variable amounts of eosinophilic to clear cytoplasm and small, uniform oval nuclei (Figs. 3A–D).

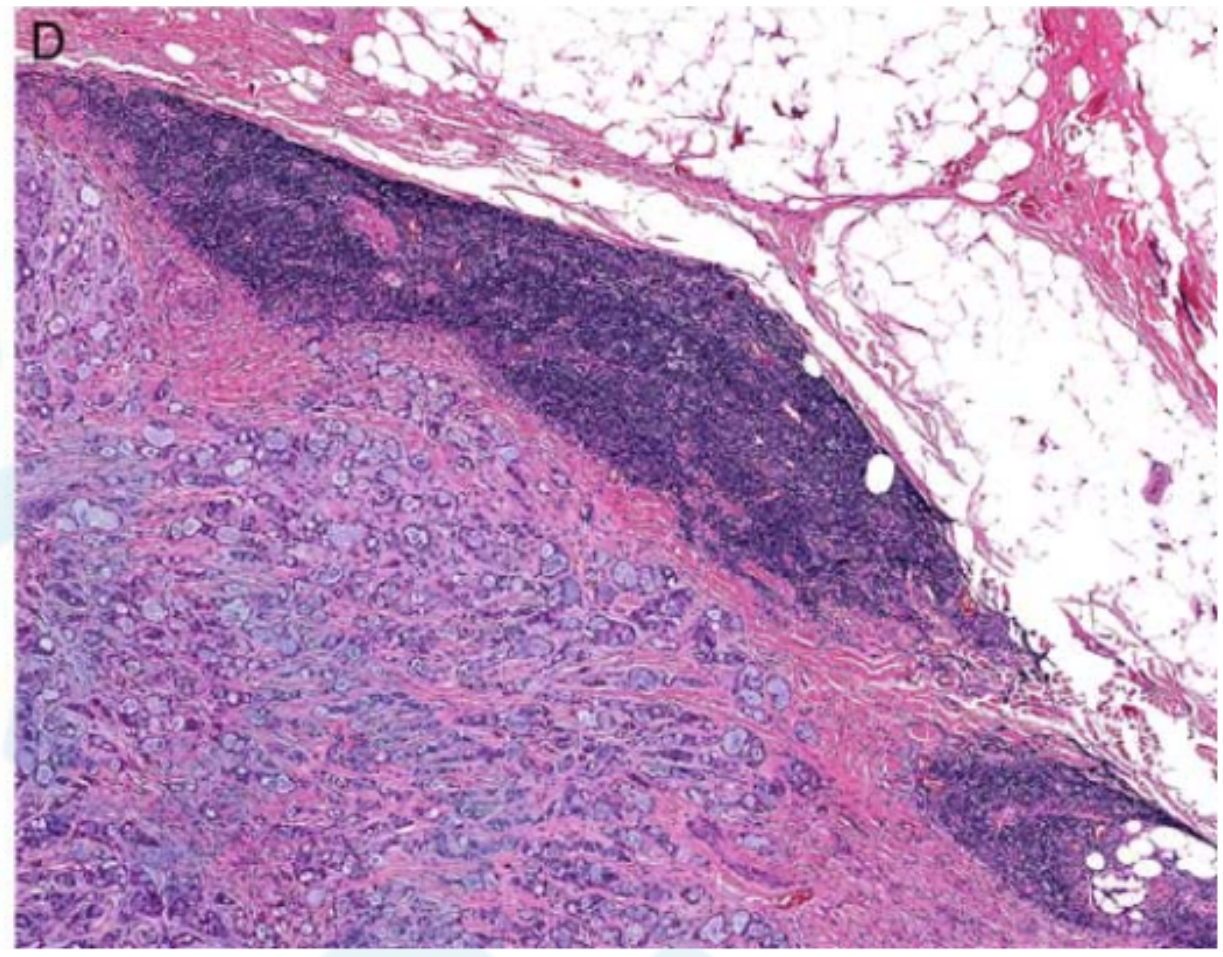
RESULTS



Uncommon features seen in the microsecretory adenocarcinomas included one case with more abundant eosinophilic cytoplasm (A), 2 cases with prominent cribriform growth (B)

RESULTS





2 cases with focal intraductal growth (C), and tumor associated lymphoid proliferation (D).

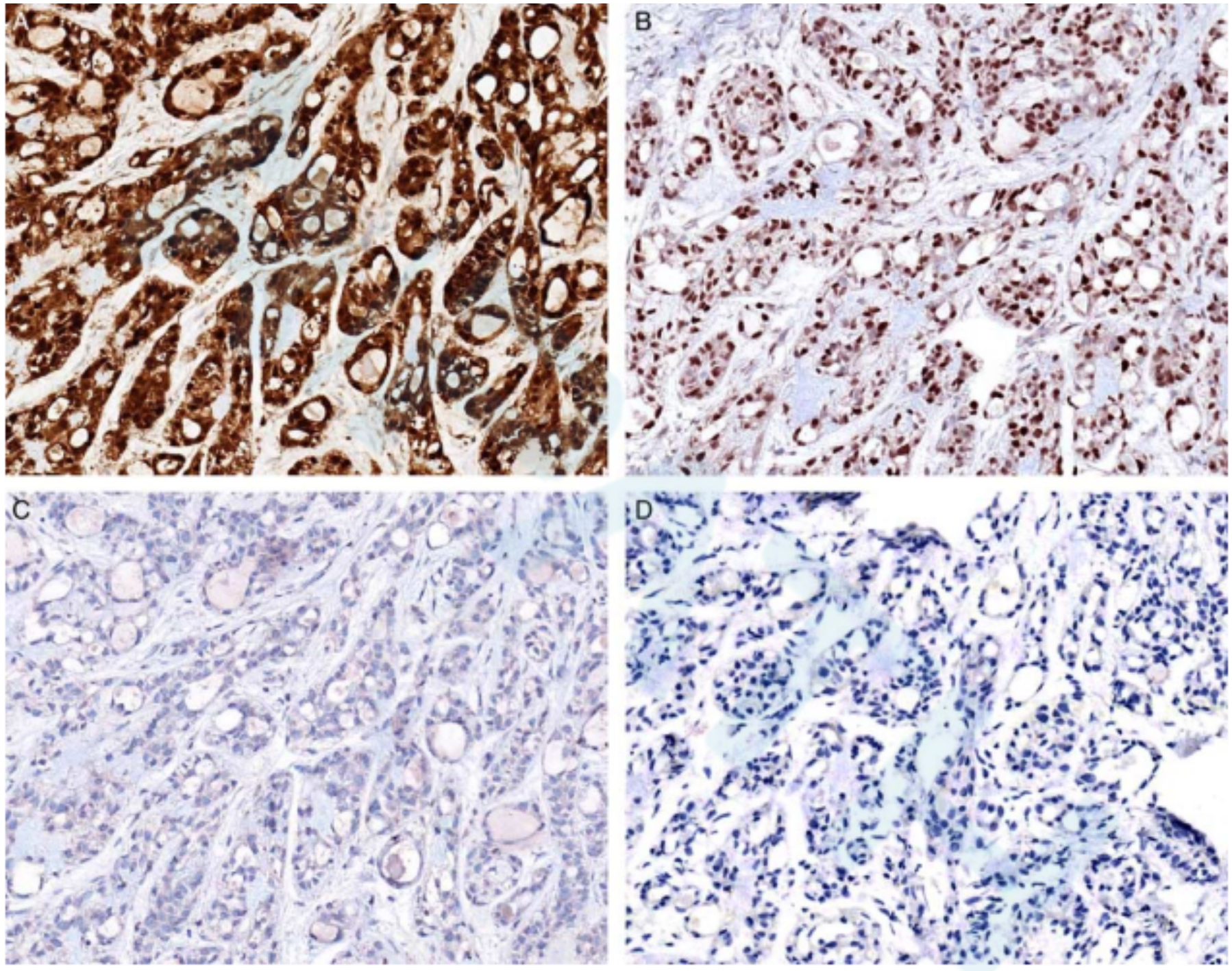
RESULTS

- Three of 5 cases demonstrated a hyalinized tumor core, and one of these cases also exhibited metaplastic bone in the tumor core.

- One case arising in the palate exhibited papillary squamous hyperplasia of the overlying surface epithelium.

- Mitotic rates were very low (0 to 1 per 10 high-power fields, mean: 0.5), and necrosis was absent.

RESULTS



Microsecretory adenocarcinoma has a consistent immunoprofile, with strong, diffuse immunoexpression for S100 (A) and p63 (B), and an absence of staining for p40 (C) or mammaglobin (D).

RESULTS

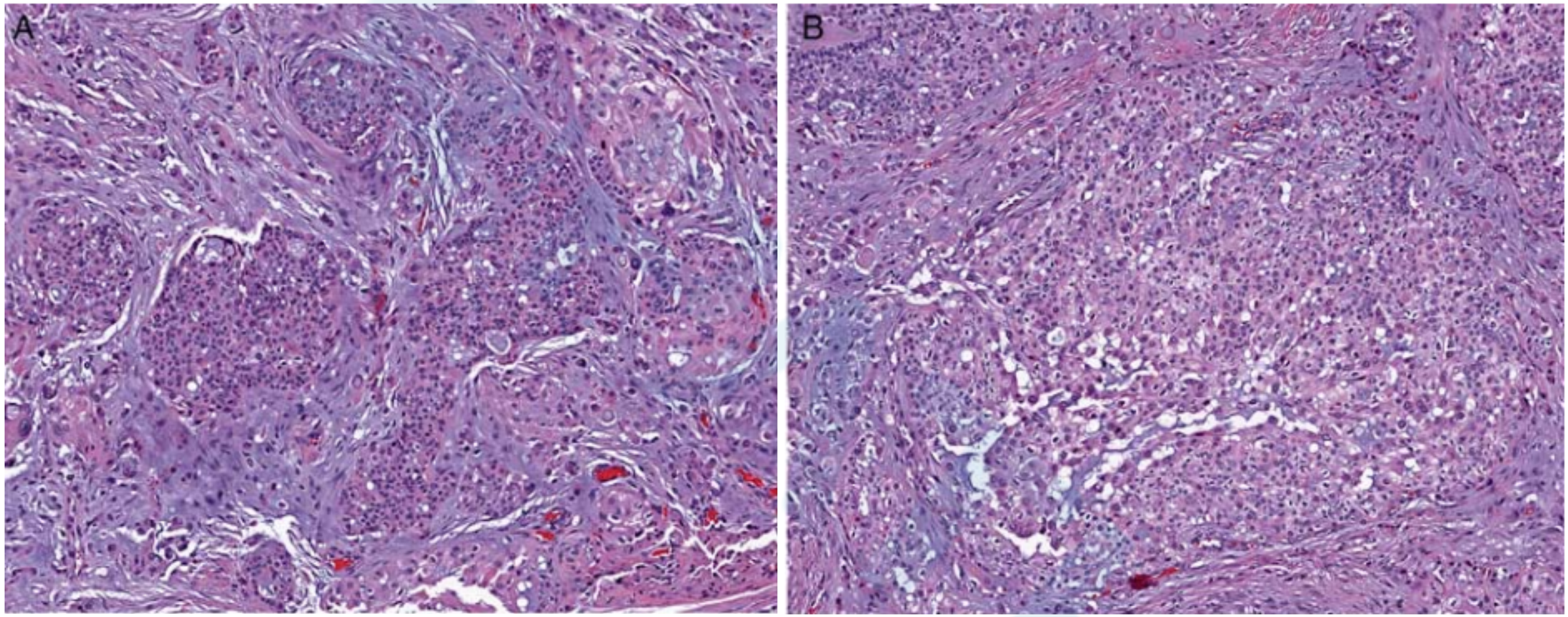
- In the control group, a single case harbored a SS18-ZBTB7A fusion involving exon 10 of the SS18 gene and exon 2 of the ZBTB7A gene .

- The SS18-ZBTB7A-positive tumor was a 2.4 cm parotid tumor from a 65-year-old woman.

- The tumor did have some overlapping features with the MEF2C-SS18-positive cases.

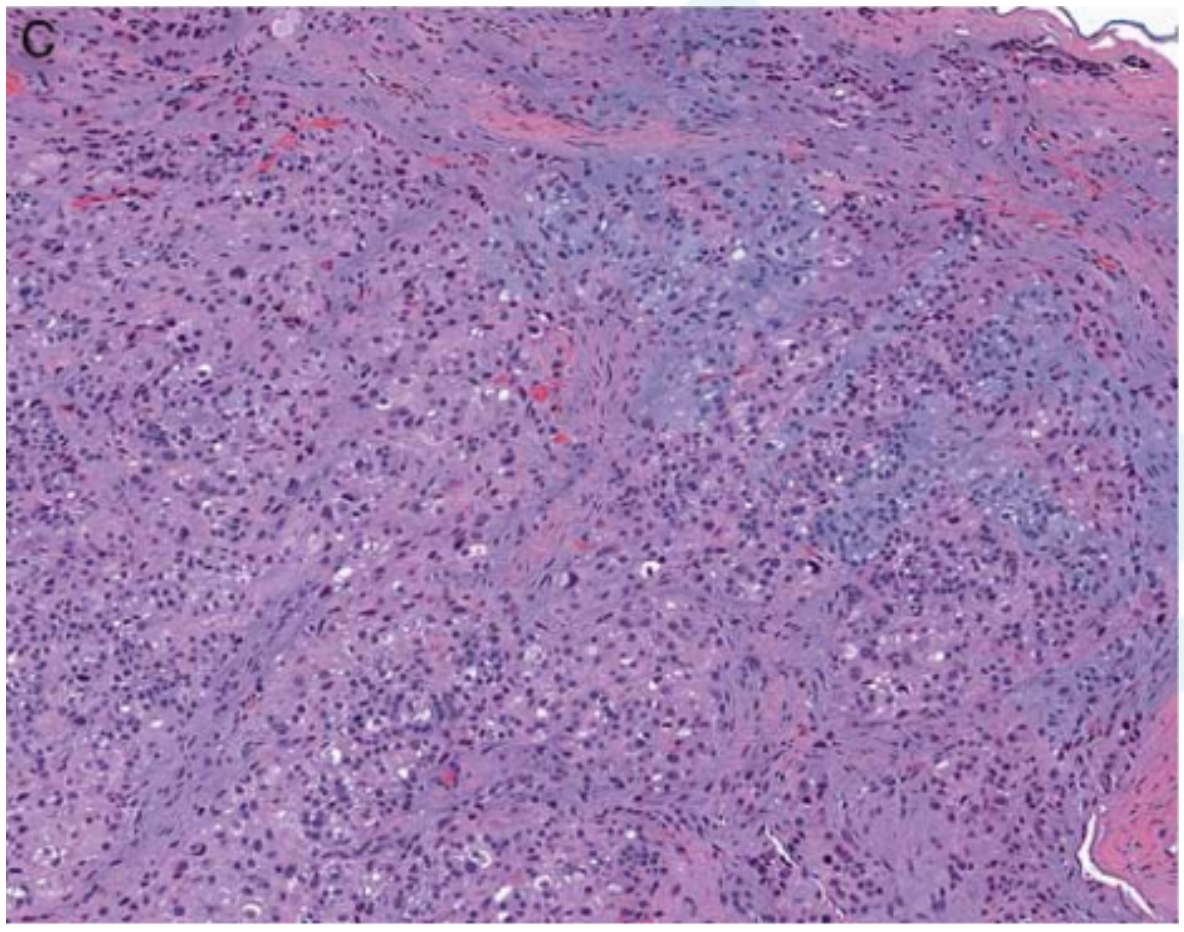
- This tumor was also infiltrative at its edge, had a cellular fibromyxoid stroma, bland cellular features, focal basophilic intraluminal secretions, and avariety of architectural growth patterns.

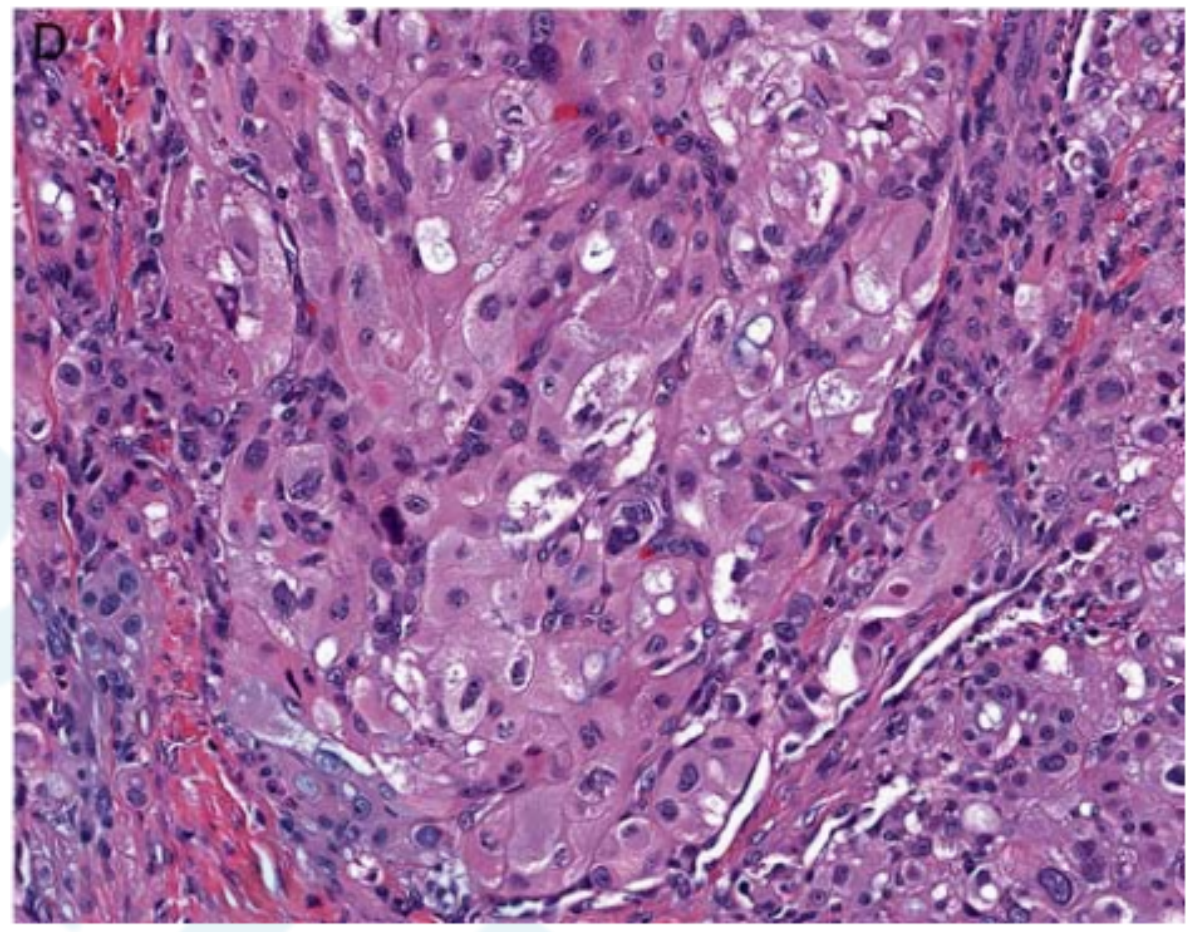
RESULTS



In limited foci, it resembled cribriform foci of microsecretory adenocarcinoma (A), but it demonstrated prominent solid (B)

RESULTS





C.Single cell patterns were more prominent. D.It demonstrated patchy areas with increased cellular pleomorphism and oncocytic morphology, with increased granular, eosinophilic cytoplasm.

By immunohistochemistry, this tumor was strongly S100 positive and negative for calponin, SMA, and mammaglobin. It was focally positive for both p63 and p40.

DISCUSSION

microsecretory adenocarcinoma

- **histology**: It exhibits consistent, unique histologic features, with a monophasic population of tumor cells containing eosinophilic to clear cytoplasm and small, uniform oval nuclei, growing as infiltrative microcysts and cords with intraluminal secretions and cellular fibromyxoid stroma.

- **immunophenotype**: diffuse S100 and p63 expression in the absence of p40, SMA, or mammaglobin.

- **molecular pathology**: MEF2C-SS18 fusions.

DISCUSSION

- Moreover, because of a lack of follow-up information in this study, the behavior of microsecretory adenocarcinoma remains to be defined.

- While it has the histologic appearance of a low-grade malignancy, this will need to be confirmed in subsequent studies.

- At present, it would seem prudent to manage microsecretory adenocarcinoma in a similar manner to other low-grade salivary carcinomas, complete resection with negative margins.

DISCUSSION

one low-grade adenocarcinoma NOS in the control group

- SS18-ZBTB7A fusion
- histologic and immunohistochemical overlap
- lacked the p63+/p40− immunophenotype

It thus remains unclear based on one case if SS18-ZBTB7A represents an alternate gene fusion for microsecretory adenocarcinoma or a distinct tumor, and additional cases will be required to make this determination.

TABLE 2. Differential Diagnosis of Microsecretory Adenocarcinoma

	Growth Pattern	Intraluminal Secretions	Stroma	Cytologic Features	Cell Type(s)	S100	Mamma-globin	p63/p40	Molecular
Microsecretory adenocarcinoma	Microcystic and cord-like, occasionally cribriform	Extensive, basophilic	Cellular and fibromyxoid	Flattened cells, eosinophilic to clear cytoplasm, monotonous oval nuclei	Ductal	Diffuse +	–	+/–	*MEF2C-SS18*
Secretory carcinoma	Variably microcystic, follicular, solid, papillary, cystic	Extensive, eosinophilic or basophilic	Typically minimal, occasionally sclerotic	Abundant eosinophilic cytoplasm, monotonous oval nuclei	Ductal	Diffuse +	+	Variable/–	*ETV6* rearrange-ments
Polymorphous adenocarcinoma (classic or cribriform adenocarcinoma types)	Variably cord-like, tubular, solid, papillary, cribriform, frequent whorls around nerves	Uncommon	Often myxoid	Moderate eosinophilic to clear cytoplasm, monotonous oval nuclei, sometimes optically clear	Ductal	Diffuse +	Variable	+/–	*PRKD1, 2,* or *3* rearrange-ments or mutations
Tubular adenoid cystic carcinoma	Mostly tubular, focally cord-like and cribriform	Common, basophilic	Typically hyalinized	Minimal eosinophilic to clear cytoplasm and hyperchromat-ic, angulated nuclei	Ductal and myoepithe-lial	Patchy +	–	Patchy +/+	*MYB* or *MYBL1* rearrange-ments
Sclerosing microcystic adenocarcinoma	Microcystic and cord-like	Extensive, eosinophilic	Extensive, sclerotic or fibrous	Minimal eosinophilic cytoplasm, uniform round to oval nuclei	Ductal and myoepithe-lial	Patchy +	Unknown	Patchy +/+	Unknown

谢谢大家