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Ectomesenchymal Chondromyxoid Tumor

A Neoplasm Characterized by Recurrent RREB1-MKL2 Fusions

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目录 CONTENTS

BACKGROUND

01 背景知识

外胚间叶软骨黏液瘤

Ectomesenchymal Chondromyxoid Tumor（ECT）

- 定义：一种良性的间叶肿瘤，由表现为肌上皮的细胞组成。
- ICD-O编码： 8982/0
- 同义词：肌上皮瘤
- 流行病学：1995年首次有19例病例报道。患者年龄7-78岁，平均37岁，无明显性别偏好。
- 临床表现：缓慢生长的（一般＜2cm）黏膜下无痛性肿块，因其所含软骨成分的多少，质地可表现为柔软、中等和较硬。
- 发病部位：几乎集中出现在舌背面前部，在舌后部及硬腭也均有报道。

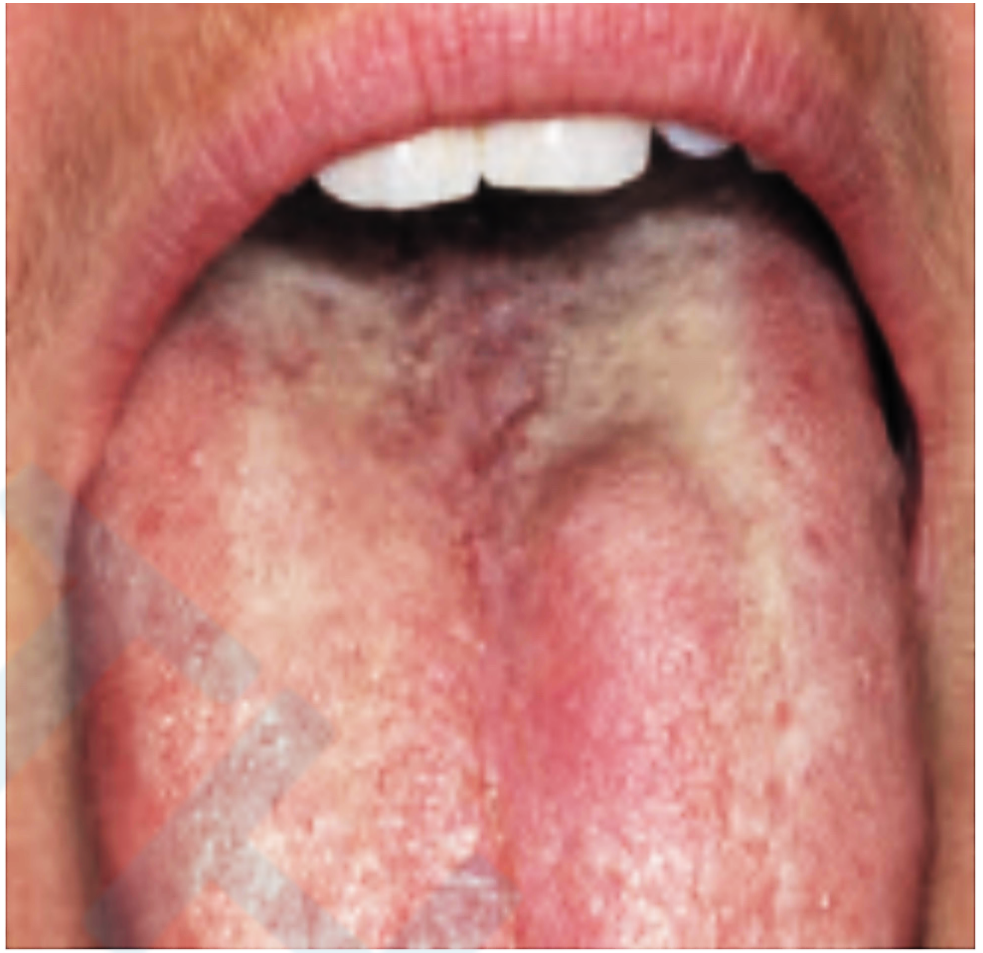


Fig. 4.39 Ectomesenchymal chondromyxoid tumour of the anterior tongue presenting as a small nodule.

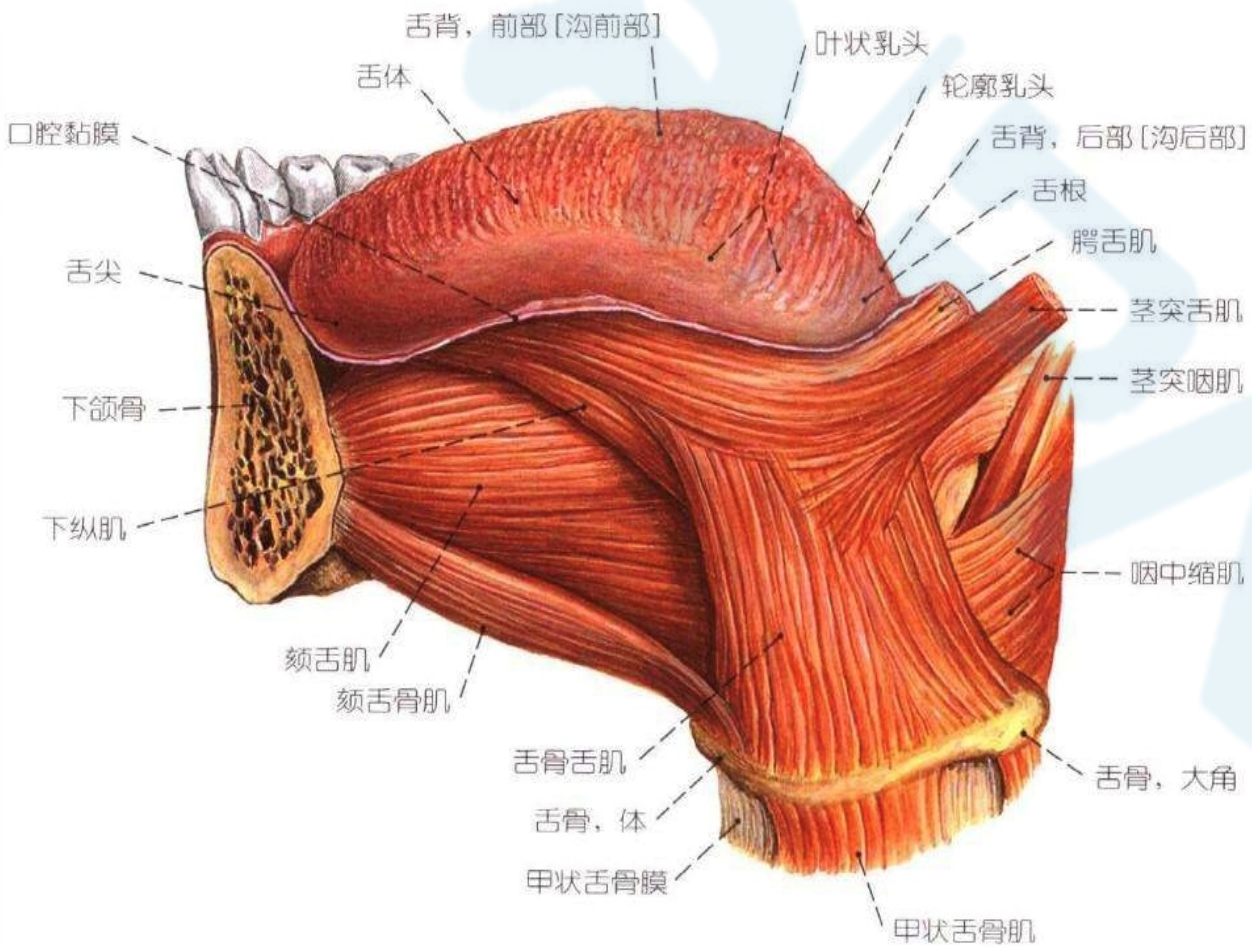
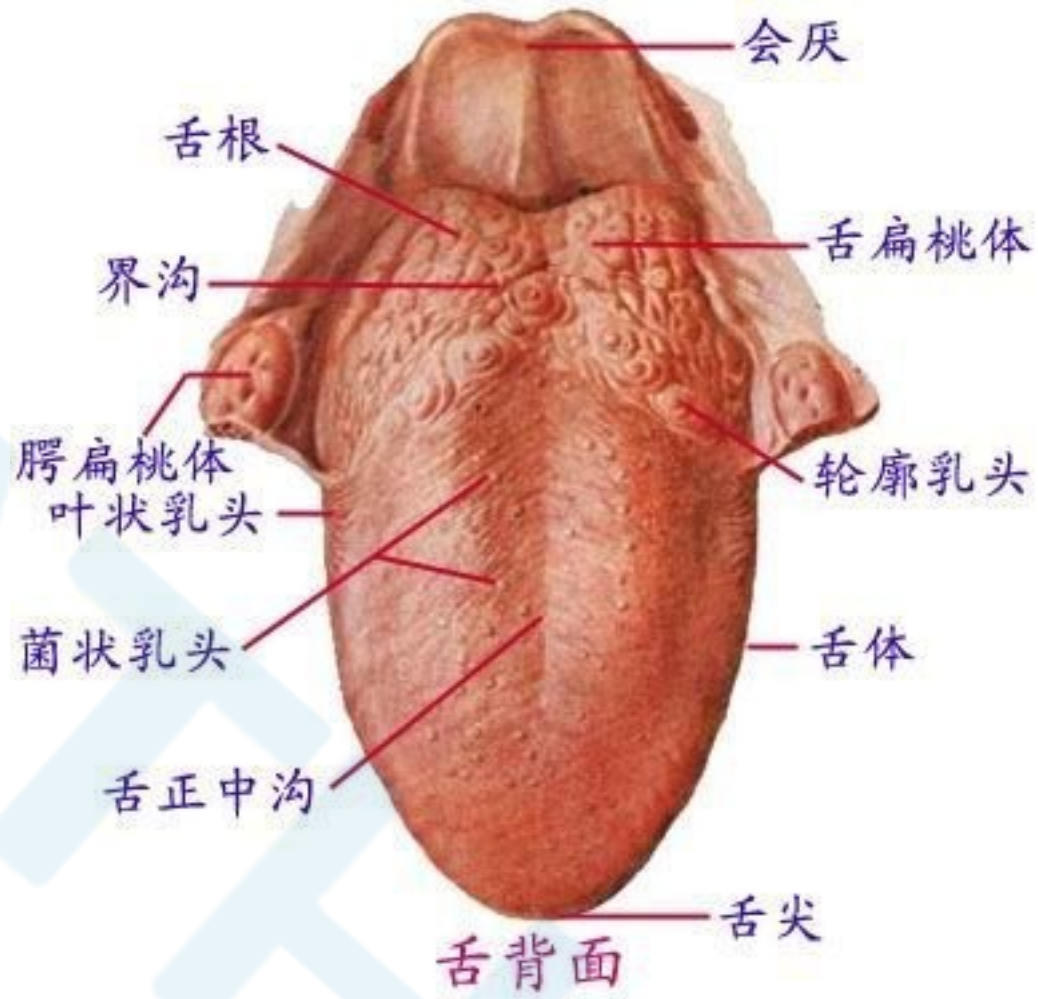


图199　舌肌；切断下颌骨；外侧面观（80%）

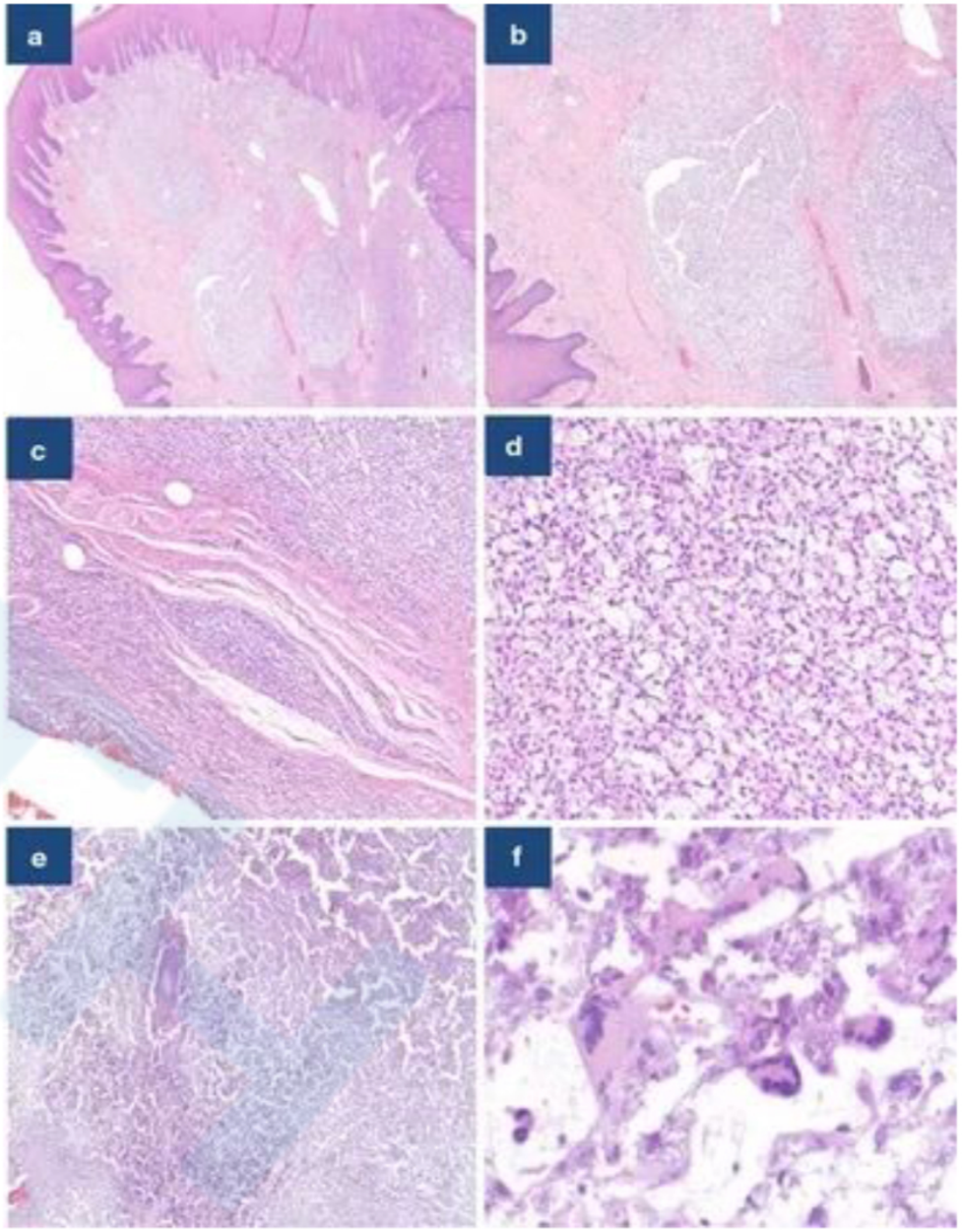


外胚间叶软骨黏液瘤

Ectomesenchymal Chondromyxoid Tumor（ECT）

➢ 镜下特点：

（1）界限清楚，无包膜。
（2）病变呈小叶状生长。
（3）细胞排列呈条索状、片状或网状。
（4）具有黏液样背景，在pH0.4及pH 2.5 AB（+）。
（5）部分病例可见软骨样物质形成，但不会有明显的软骨细胞分化。
（6）细胞核大小一致，呈圆形、卵圆形、纺锤形，胞浆为中等含量弱嗜酸性。
（7）部分细胞核可见异型性（这种异型性与恶性程度无关，可能与继发性炎症刺激及肿瘤老化相关），但核分裂少见。
（8）病变可表现为“浸润性”，当深达肌层时，可包裹肌肉生长。
（9）部分病例可观察到钙化、假包涵体及多核巨细胞。



鉴别诊断

- 局灶性黏蛋白沉积症
- 黏液潴留
- 软组织黏液瘤
- 神经鞘黏液瘤
- 骨外黏液样软骨肉瘤
- 多形性腺瘤
- 来源于小涎腺肌上皮瘤的变异

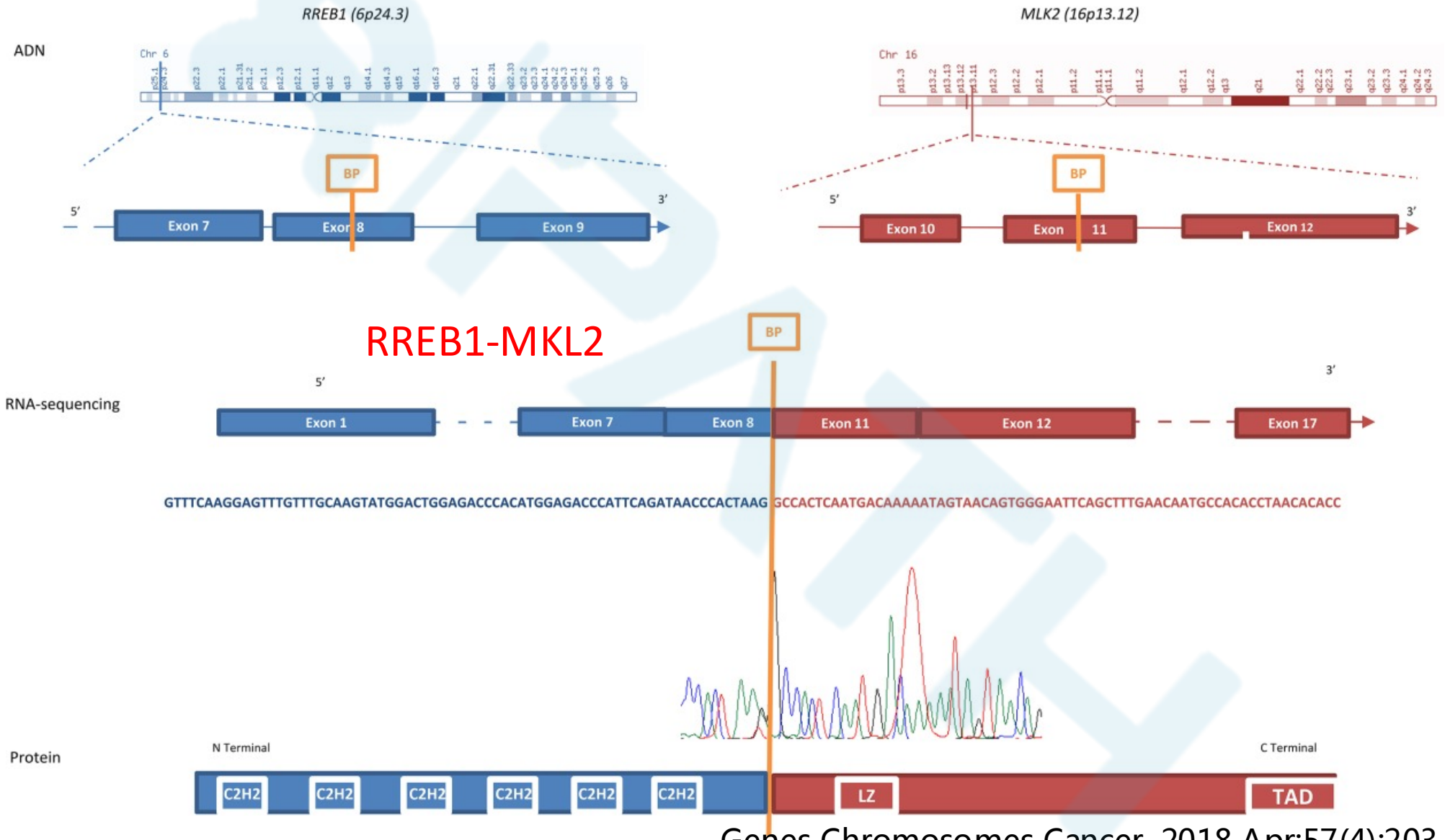
（WHO 2006）

外胚间叶软骨黏液瘤 Ectomesenchymal Chondromyxoid Tumor（ECT）

- 免疫表型：

阳性表达	不确定阳性	阴性表达
GFAP、Vimentin	S-100、SMA、keratin、CD56、CD57	CD34、EMA、p63

外胚间叶软骨黏液瘤 Ectomesenchymal Chondromyxoid Tumor（ECT）



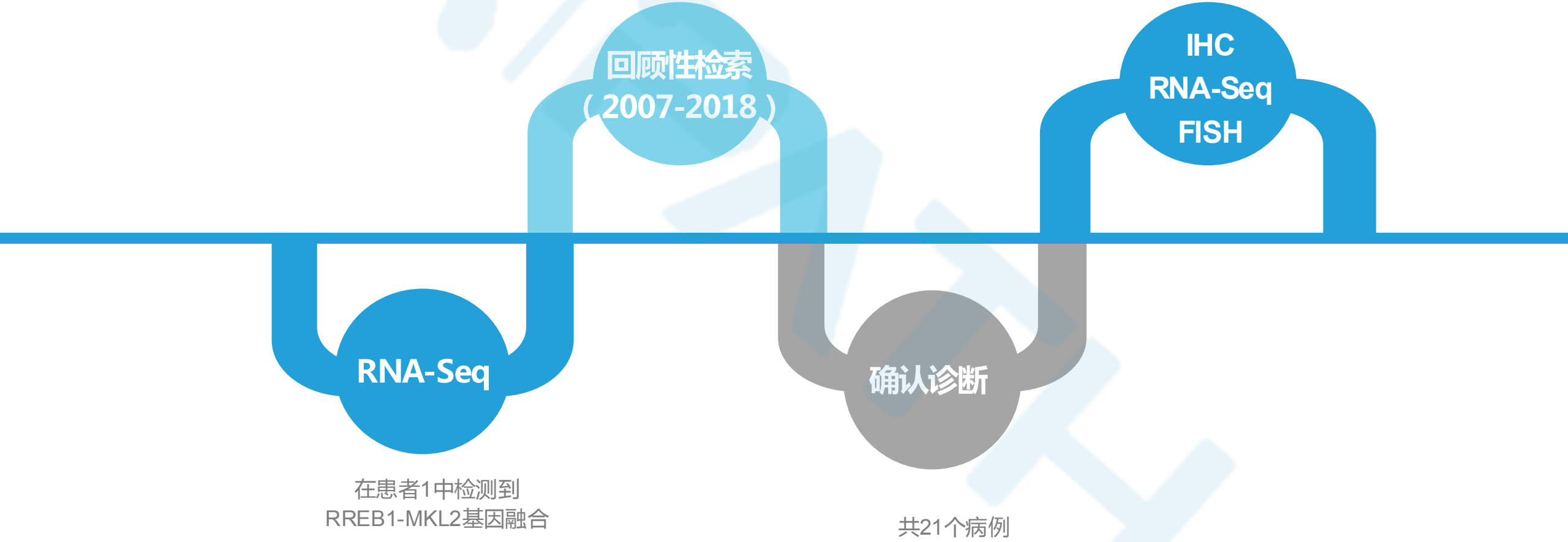
Genes Chromosomes Cancer. 2018 Apr;57(4):203-210.

02

MATERIALS AND METHODS

材料和方法

MATERIALS AND METHODS



在患者1中检测到
RREB1-MKL2基因融合

共21个病例

TABLE 1. Clinical and Demographic Information

Patient	Age (y)	Sex	Location	Size and Clinical Findings
1	31	F	Tongue, NOS	0.9 cm. Excised with negative margin
2	48	M	Tongue, dorsal, tip	0.6 cm. Shave biopsy. No evidence of recurrence at 1 y
3	39	F	Tongue, left dorsal, posterior	1.1 cm. <2 mo follow-up
4	54	F	Tongue, dorsal, anterior	1.4 cm. Re-excision, with positive margin. No report of recurrence
5	54	M	Tongue, dorsal	Not available
6	23	M	Tongue, left anterior	3.0 cm. No evidence of recurrence at 2 y
7	13	F	Tongue, right midline dorsal	2.0 cm soft mass
8	45	F	Tongue, left dorsal	Size not specified. 6-7 mo asymptomatic mass
9	54	M	Tongue, left anterior	1.2 cm. Excised with negative margins. No evidence of recurrence at 1.4 y
10	35	M	Tongue, left anterior	0.7 cm. Excised with positive margins. Recurred at 41 mo. No further recurrences after 4 y
11	14	F	Tongue, midline anterior	1.5 cm. Excised with positive margins. No evidence of recurrence after 8.5 y
12*	49	F	Tongue, dorsal lateral	2.1 cm
13*	33	F	Tongue, NOS	Not available
14	50	F	Tongue, dorsal tip	2.4 cm. Excised with negative margin. LTF
15*	53	F	Tongue, NOS	Not available
16*	59	M	Tongue, NOS	Not available
17*	31	F	Tongue, NOS	Not available
18*	51	M	Tongue, midline dorsal, anterior	2.5 cm. 15-y history before excision
19	40	F	Tongue, right dorsal, anterolateral	1.0 cm. Slow-growing lump ×3-5 mo. Margin focally positive, but no report of recurrence
20	51	M	Tongue, NOS	0.7 cm. Margin focally positive, with no report of recurrence
21	15	F	Tongue, right dorsal, posterior	0.7 cm

*Previously reported.[7,11]
F indicates female; LTF, lost to follow-up; M, male; NOS, not otherwise specified.

03

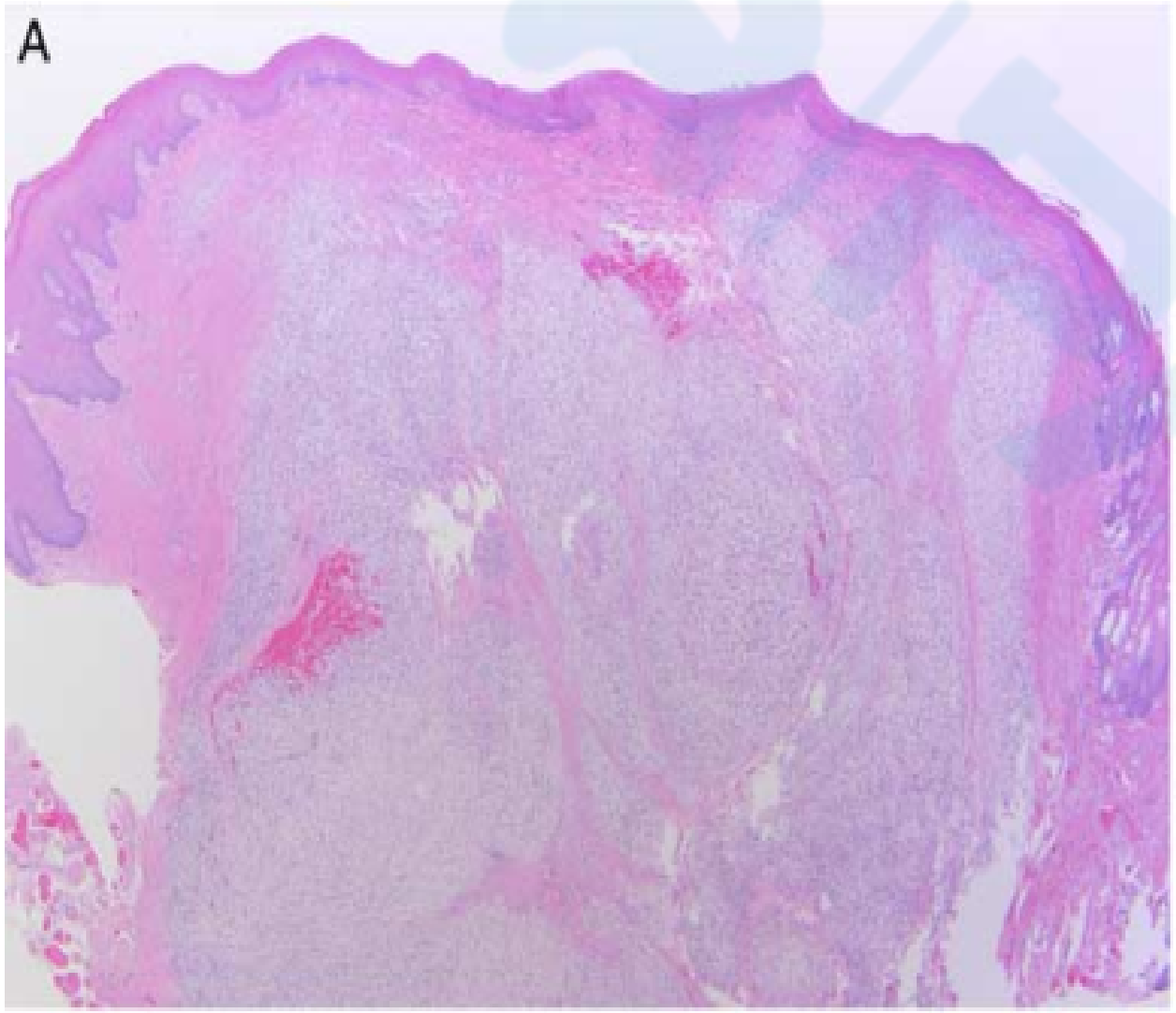
RESULTS

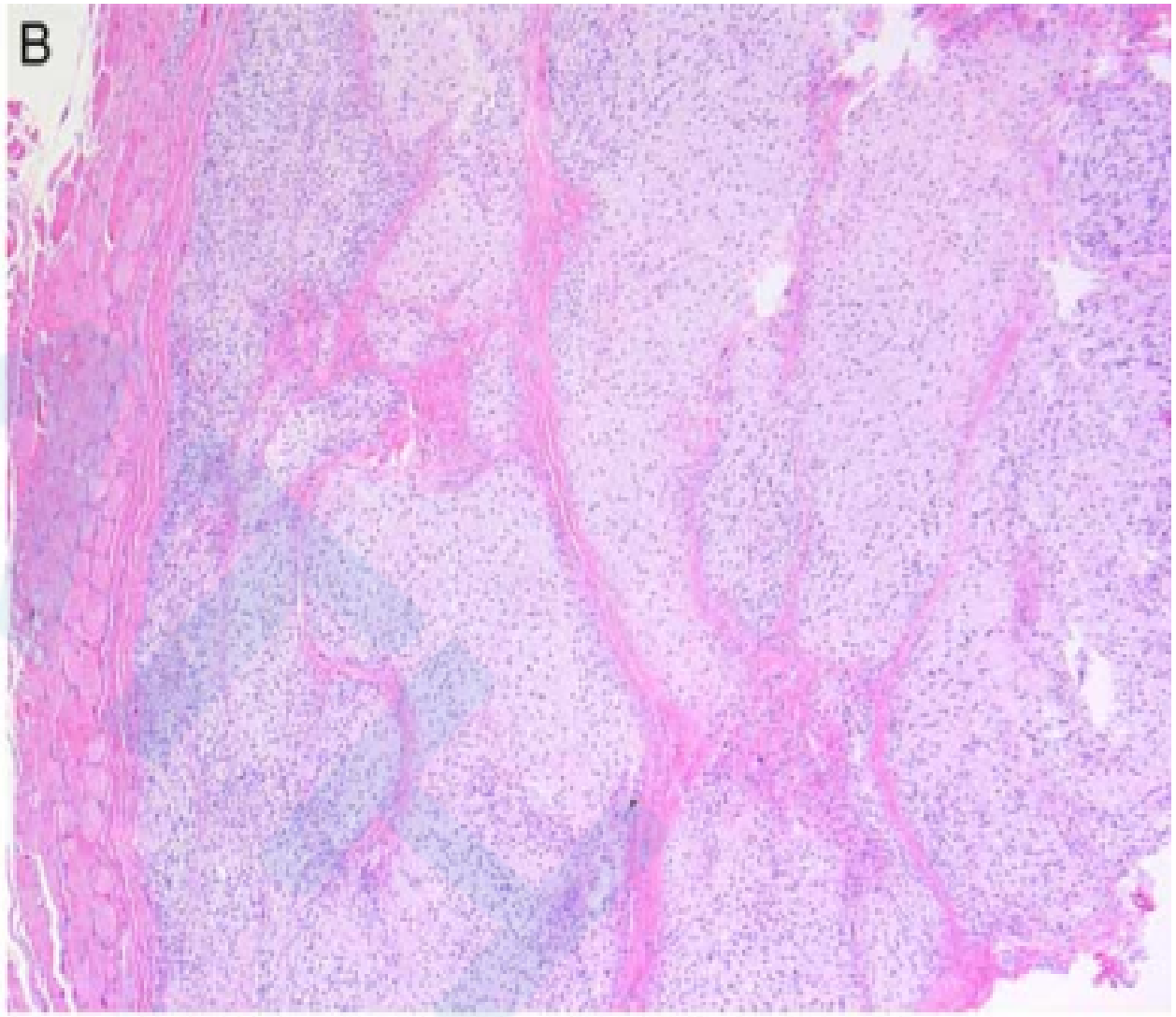
结　果

RESULTS

- 年龄：13-59岁（平均年龄40岁）
- 性别：13F：8M，比例约为1.6：1
- 部位：均发生于舌背部，大多数发生于舌前部，少部分发生于后部
- 肿瘤大小：0.6-3cm（平均1.5cm）
- 预后：大多数病例简单切除治疗后治愈。（尽管有一部分病例在显微镜下观察到边缘阳性，但有随访记录的病例中只有一例复发）

RESULTS





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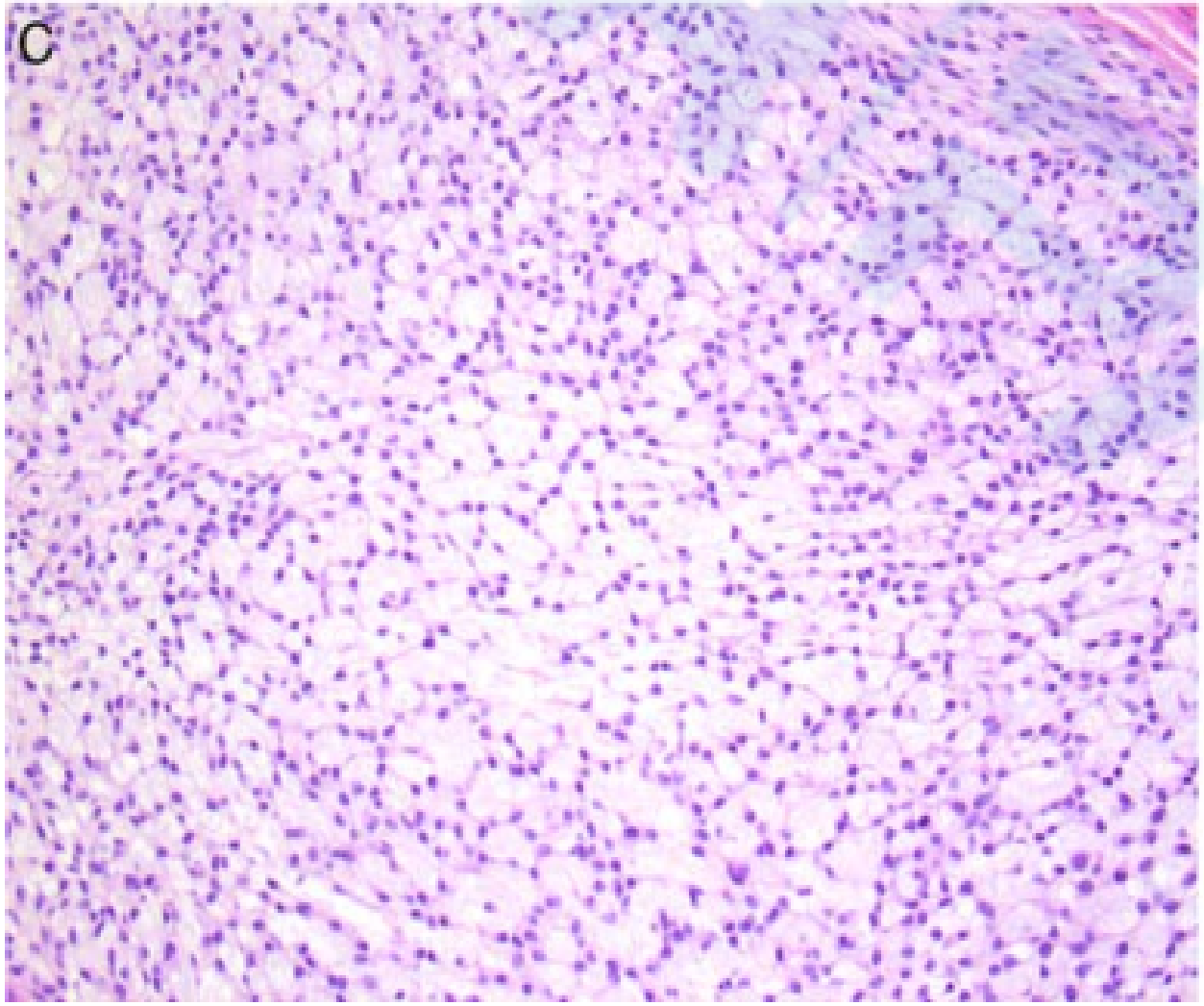

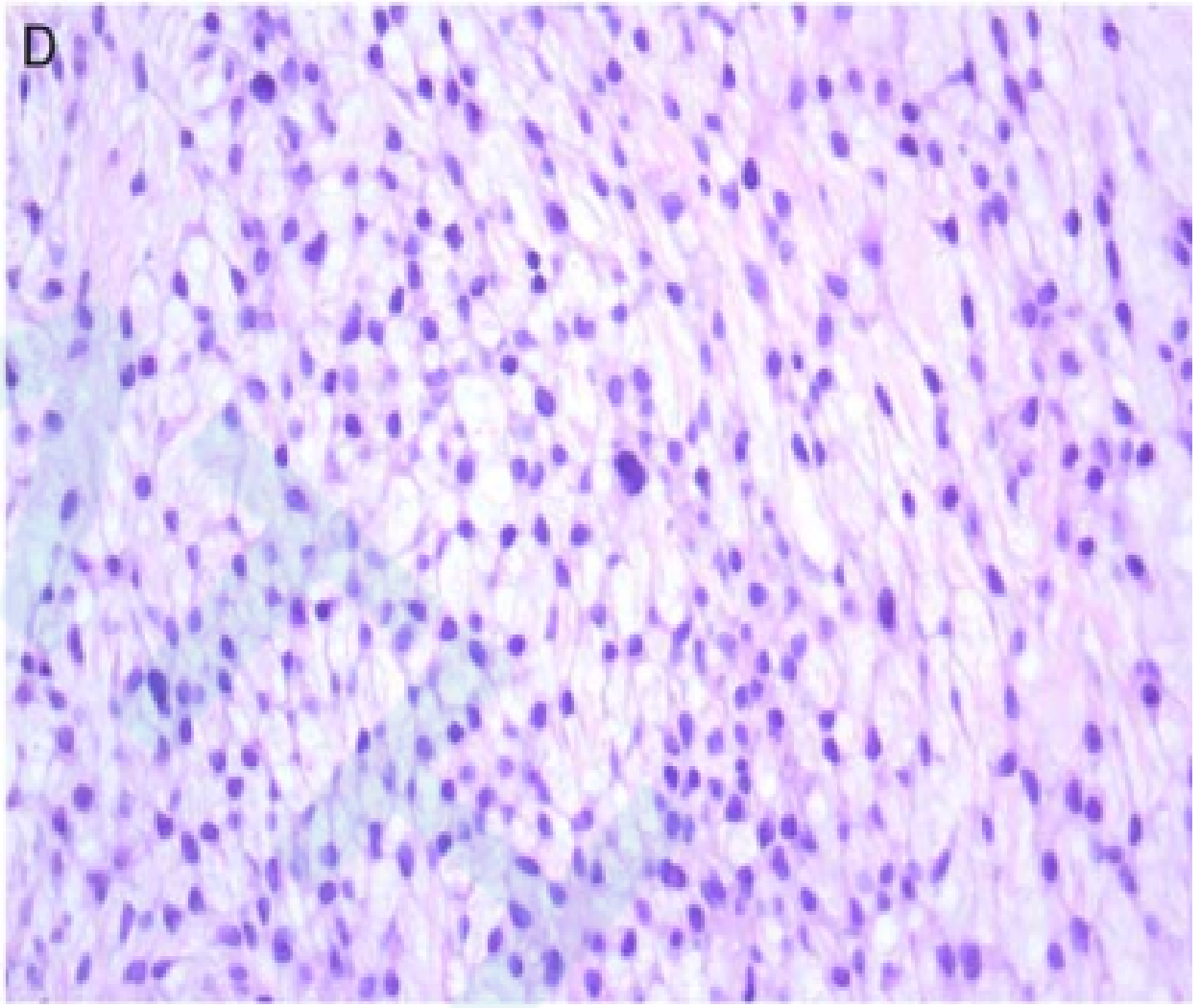

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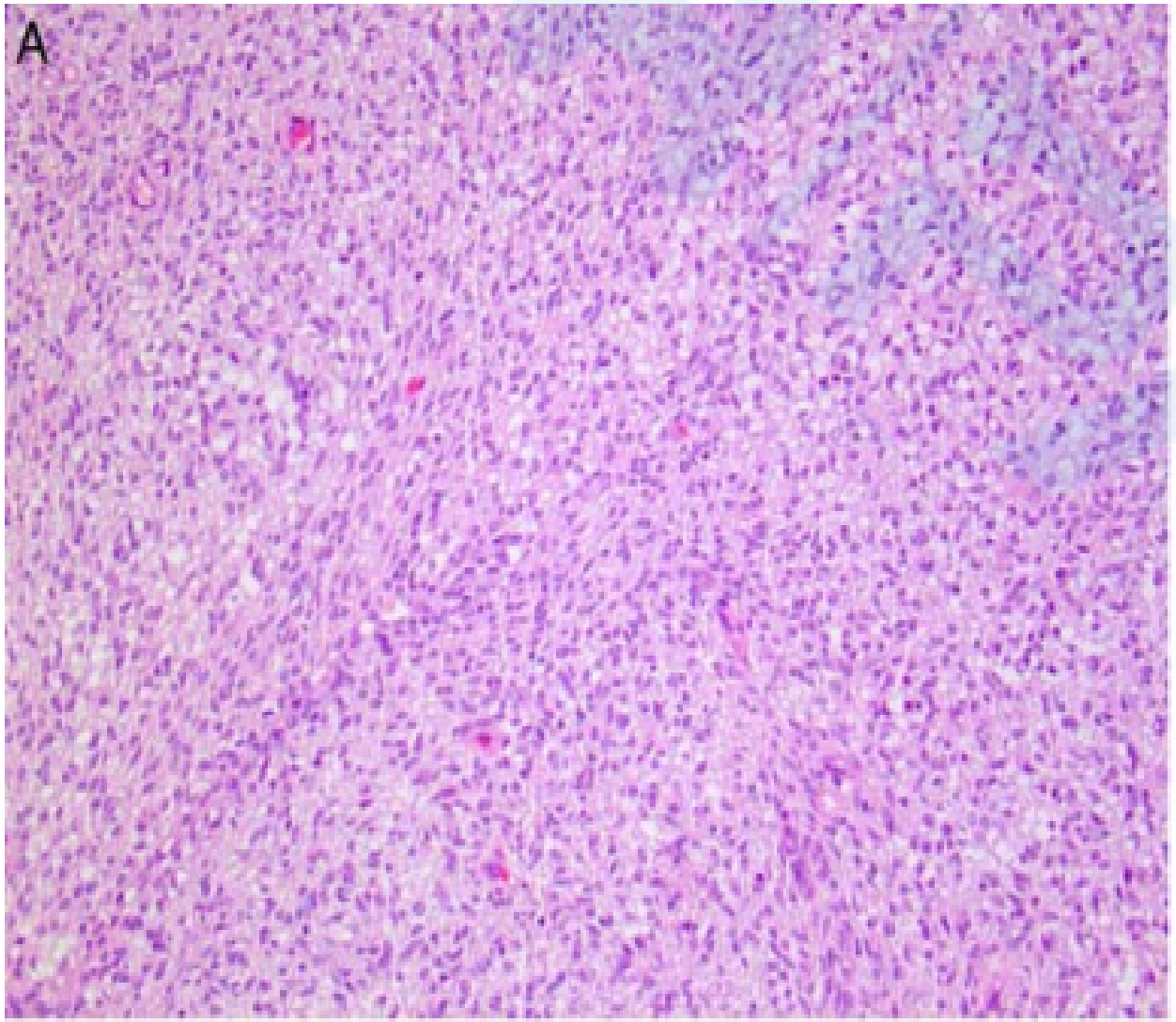

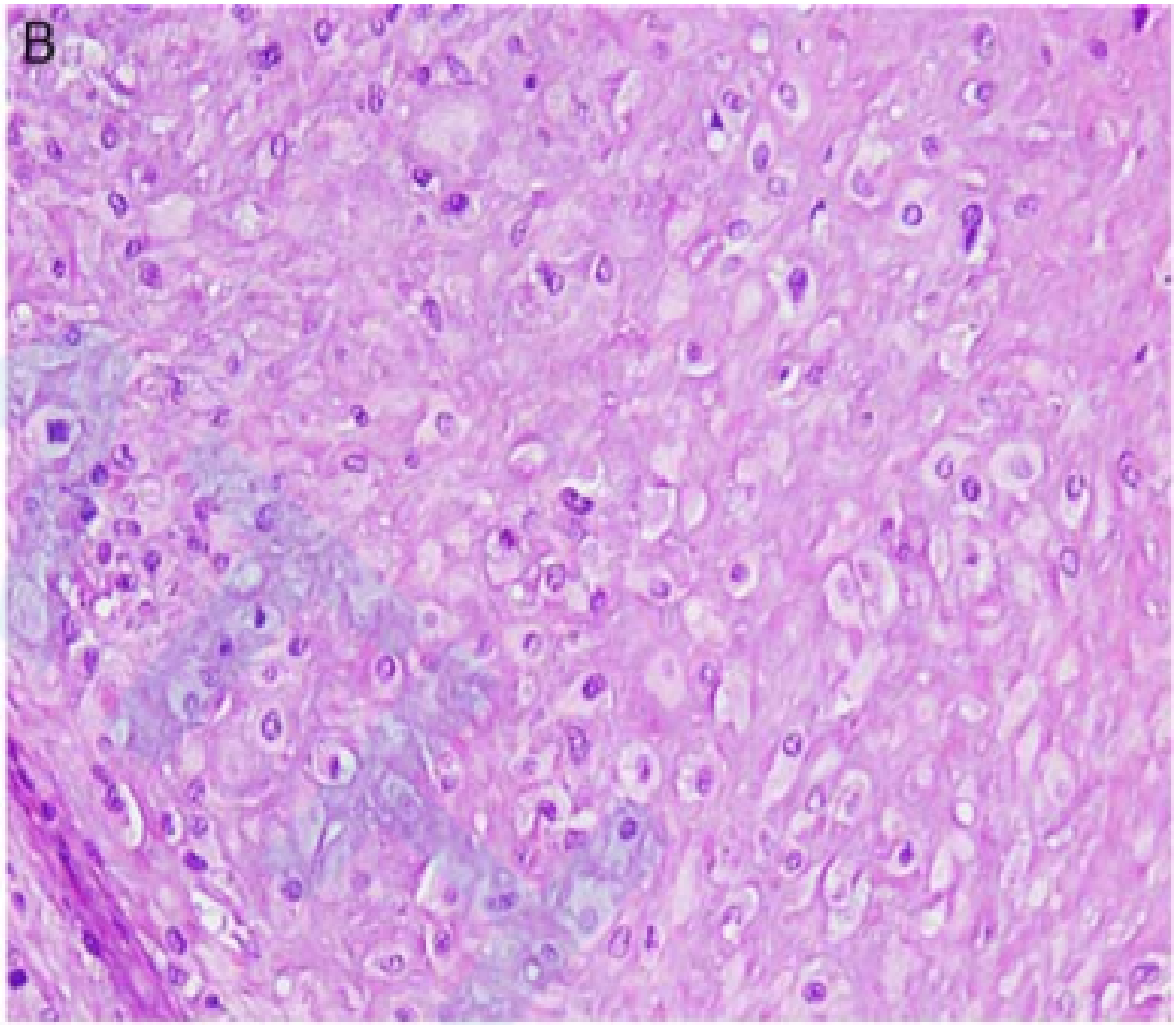

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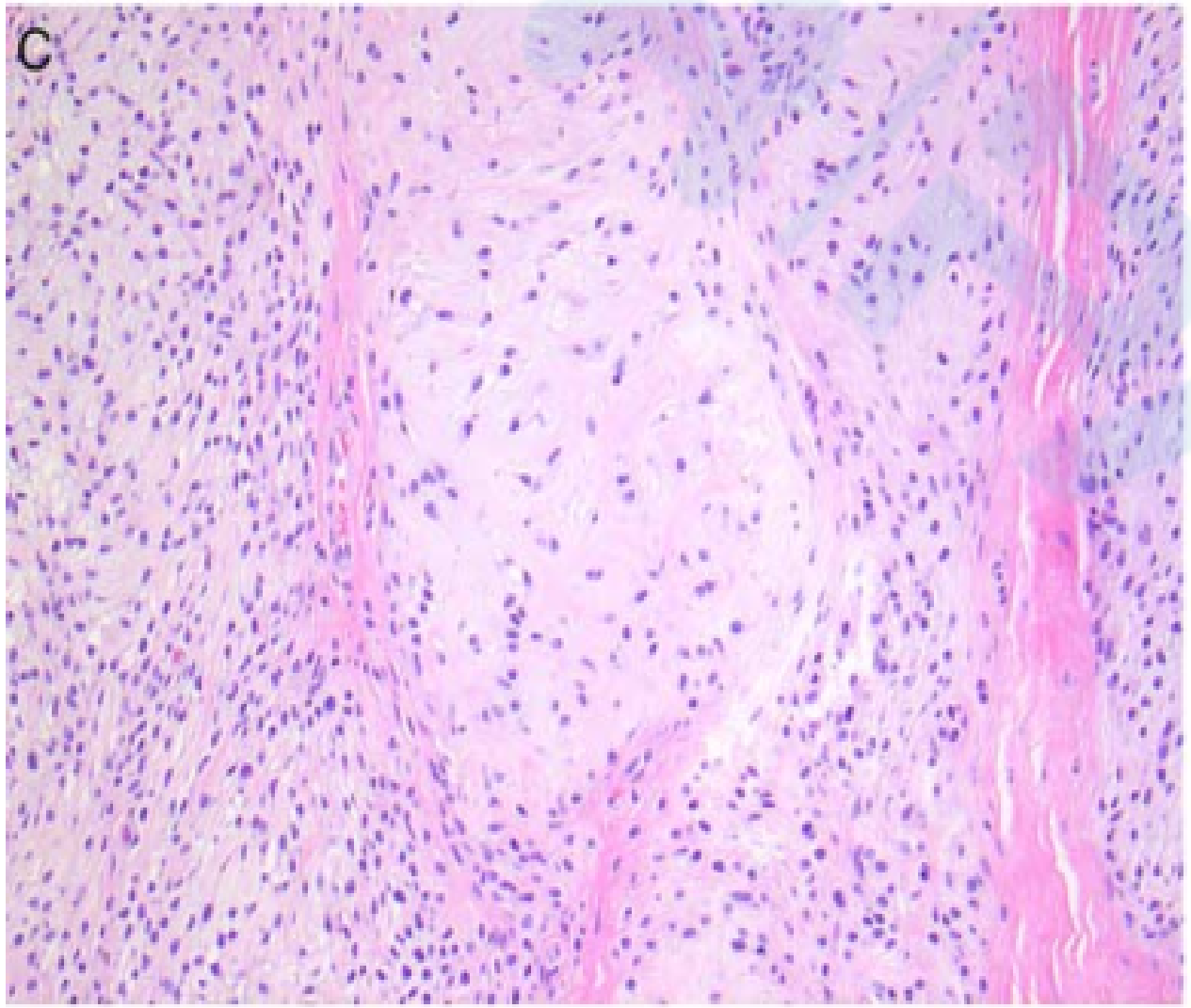

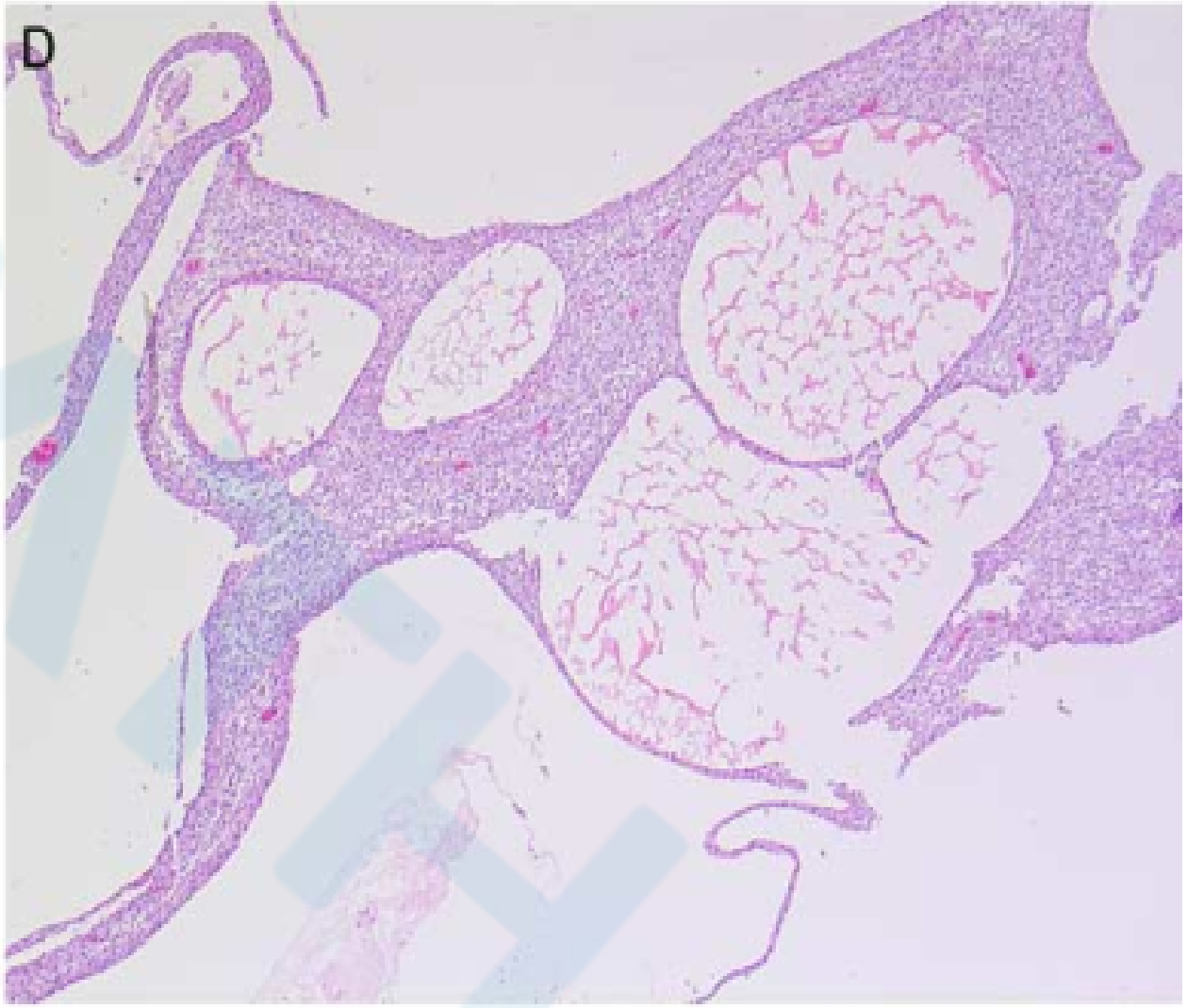

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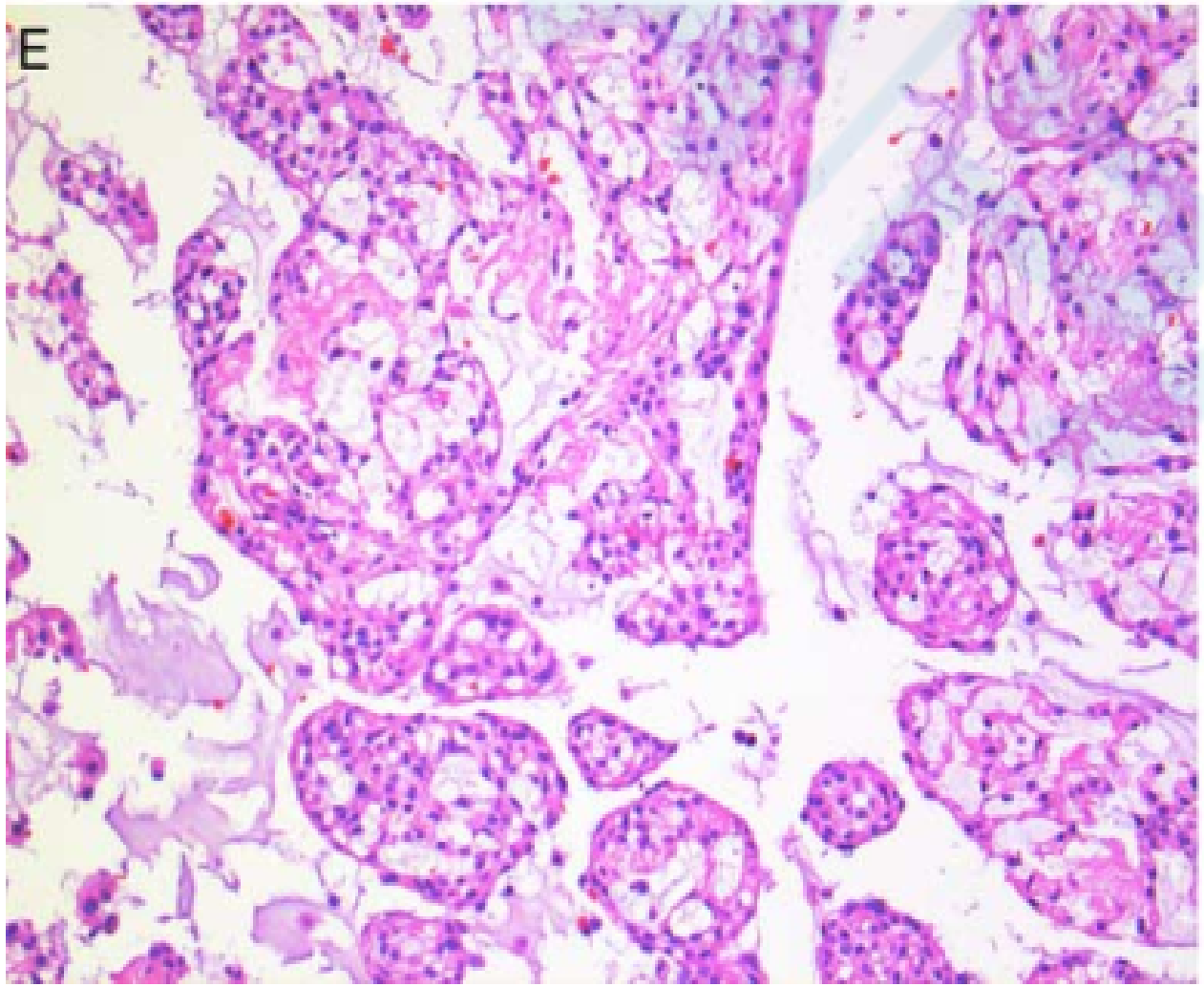
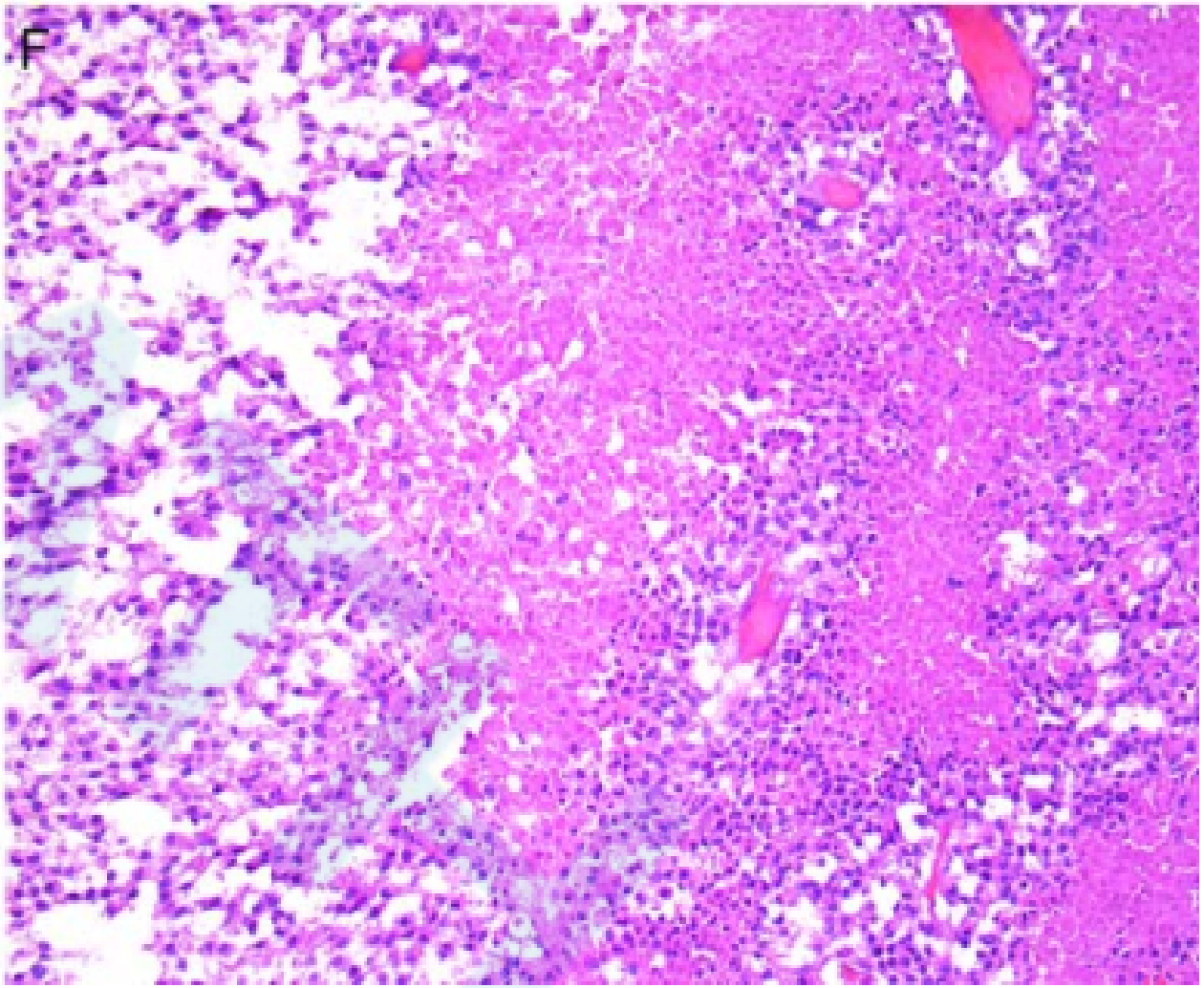




- 几乎所有病例均有与周围界限清楚的边界，且呈推挤性的生长方式，有几例局灶浸润至周围骨骼肌；
- 被覆完整的鳞状上皮；
- 多分叶，小叶由内源性间质分隔或由纤维分隔；呈片状、梁索状、网状排列，束状、微囊性及乳头状少见，间质偶尔有出血及含铁血黄素沉积；
- 细胞从多角形到纺锤形不等，胞浆透明、嗜酸或轻度嗜碱性，核圆形至卵圆形，深染；
- 散在细胞可出现异型性、假包涵体及双核，核分裂象少见，1-2个/HPF

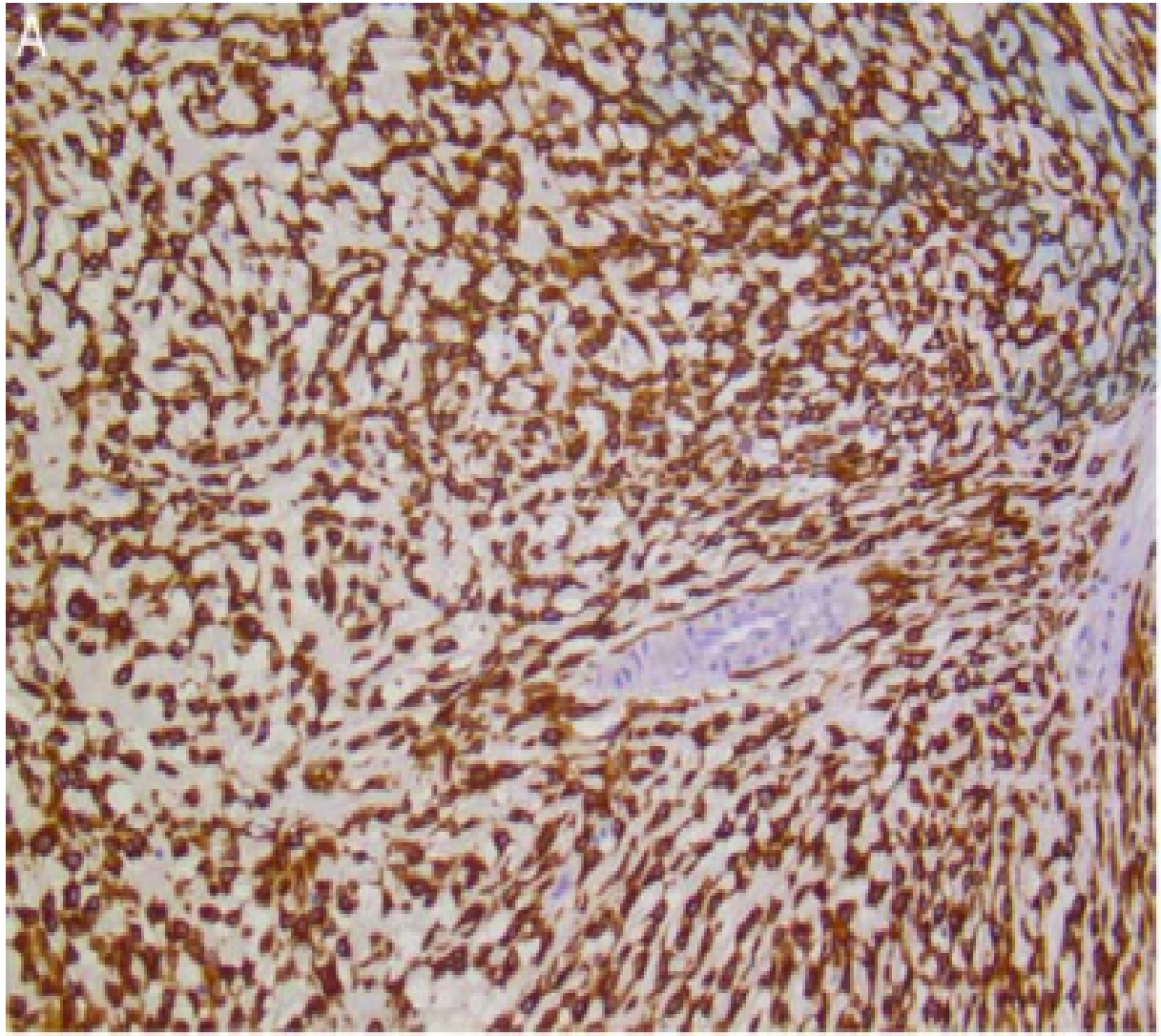
TABLE 2. Summary of Immunohistochemical and Molecular Attributes of Ectomesenchymal Chondromyxoid Tumor

	Immunohistochemistry						Molecular	
Patient	GFAP	S100	Keratin	Desmin	Myogenin	SMA	Method	Result
1	–	3+	–	1+	NP	1+	RNA-Seq	*RREB1-MKL2*
2	–	–	–	–	–	–	RNA-Seq	*EWSR1-CREM*
3	5+	5+	1+	1+	–	3+	RNA-Seq	*RREB1-MKL2*
4	4+	3+	1+	–	–	1+	RNA-Seq	Negative
5	NP	NP	NP	NP	NP	NP	RNA-Seq	*RREB1-MKL2*
6	5+	5+	2+	1+	2+	2+	RNA-Seq	*RREB1-MKL2*
7	5+	2+	–	NP	NP	–	RNA-Seq	*RREB1-MKL2*
8	5+	3+	–	NP	NP	NP	RNA-Seq	*RREB1-MKL2*
9	1+	3+	–	–	–	3+	RNA-Seq	*RREB1-MKL2*
10	2+	3+	–	–	–	3+	RNA-Seq and FISH	*RREB1-MKL2*
11	5+	3+	2+	4+	–	2+	RNA-Seq	*RREB1-MKL2*
12	4+	2+	1+	1+	–	NP	FISH	*RREB1-MKL2*
13	5+	2+	1+	1+	–	NP	FISH	*RREB1-MKL2*
14	4+	1+	–	1+	–	NP	FISH	*RREB1-MKL2*
15	4+	NP	–	NP	–	NP	FISH	*RREB1-MKL2*
16	4+	1+	–	–	–	NP	FISH	*RREB1-MKL2*
17	2+	NP	–	NP	–	NP	FISH	*RREB1-MKL2*
18	5+	5+	2+	1+	–	3+	FISH	*RREB1-MKL2*
19	5+	2+	2+	1+	–	NP	FISH	*RREB1-MKL2*
20	4+	1+	1+	3+	1+	3+	FISH	*RREB1-MKL2*
21	5+	2+	2+	–	–	–	FISH	*RREB1-MKL2*

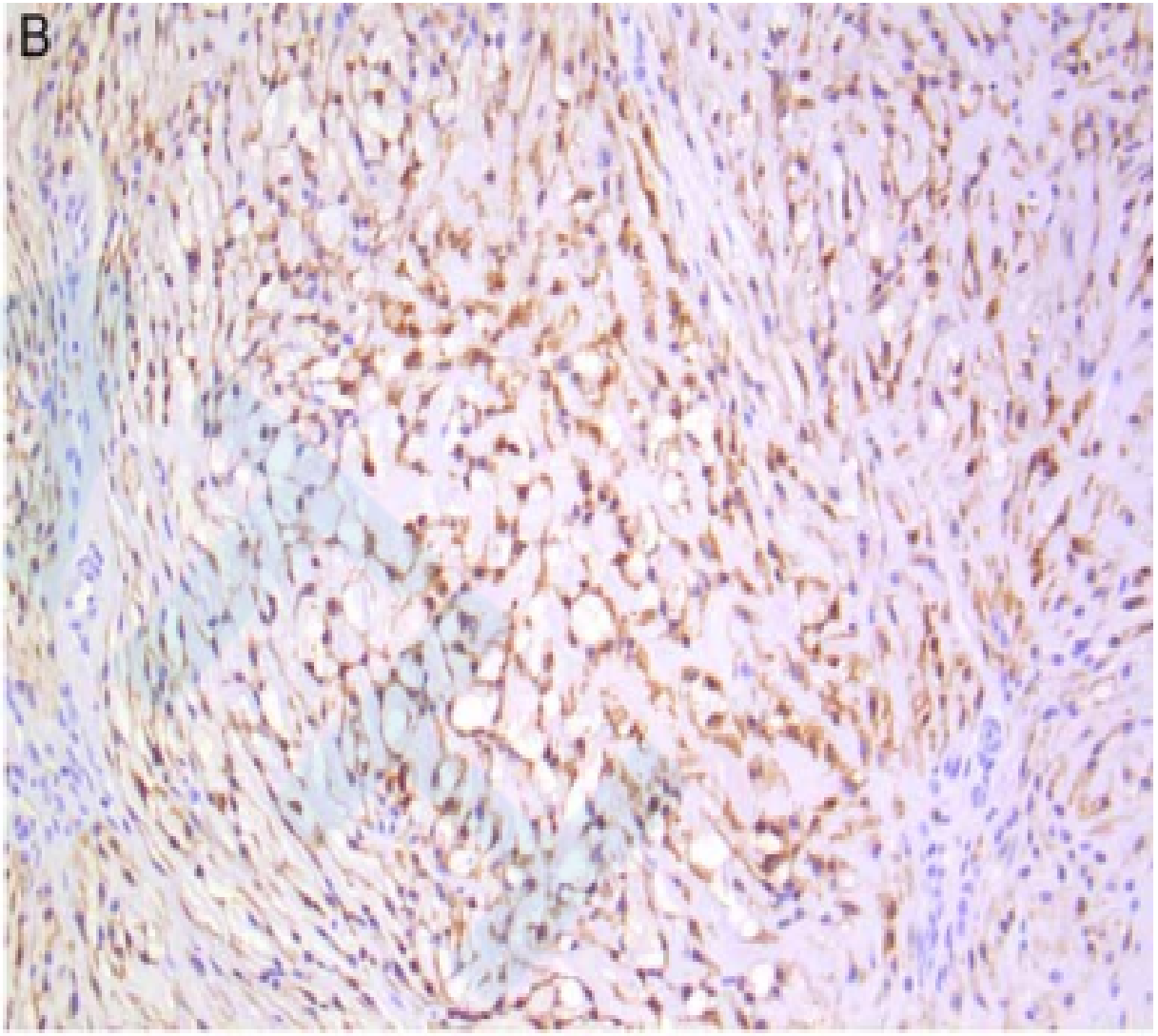
– indicates negative; GFAP, glial fibrillary acid protein; NP, not performed; SMA, smooth muscle actin.

RESULTS

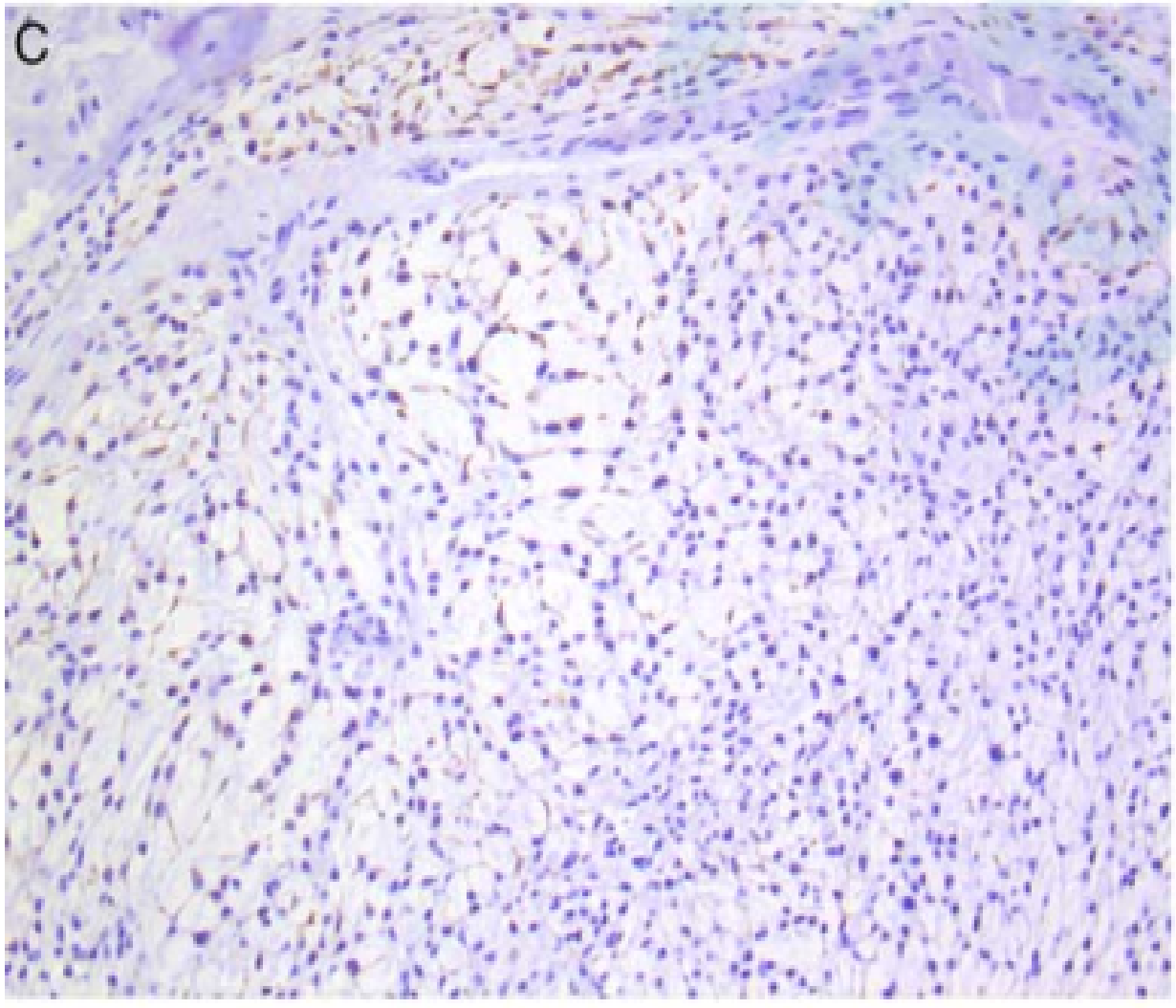
GFAP



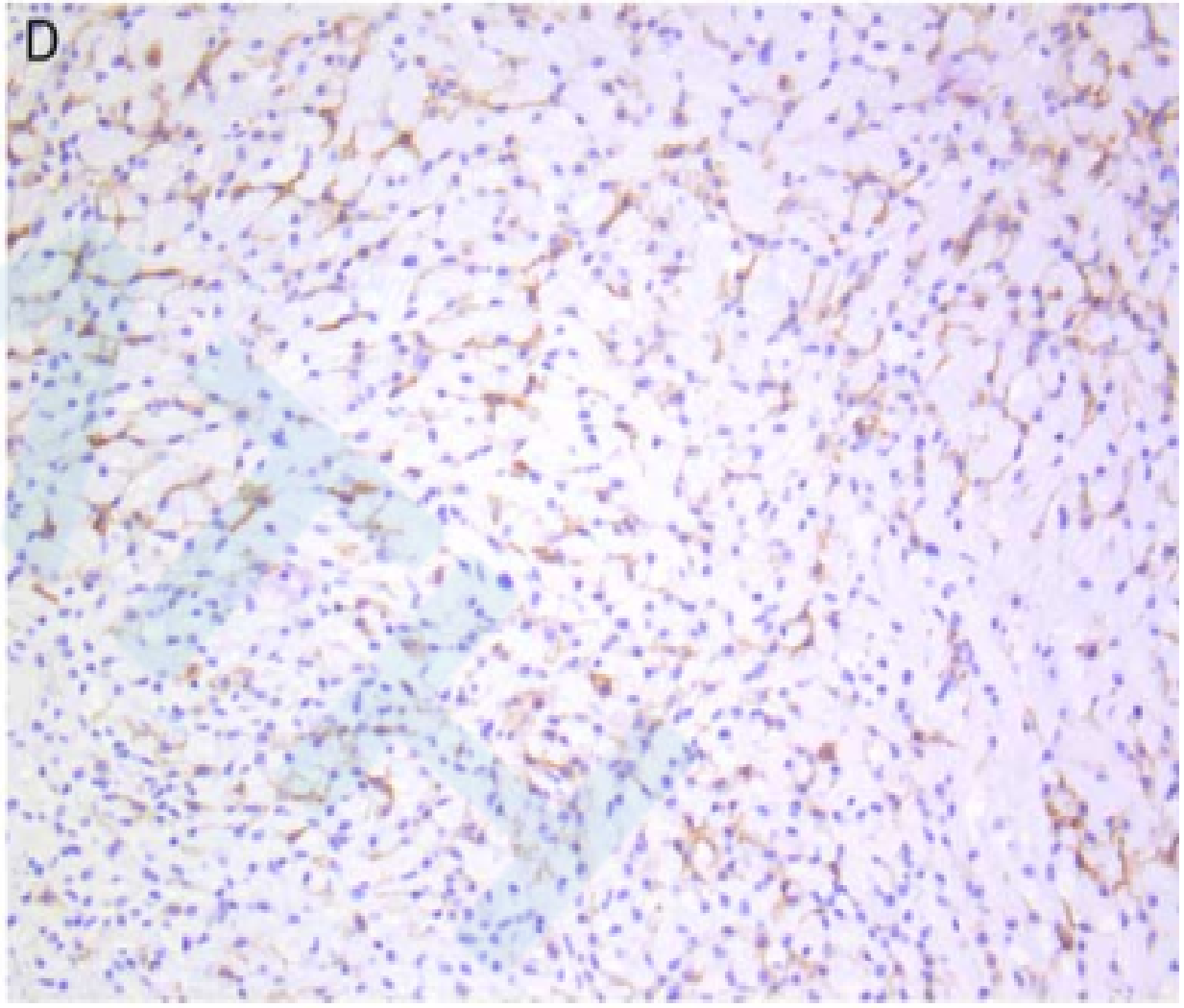
S-100



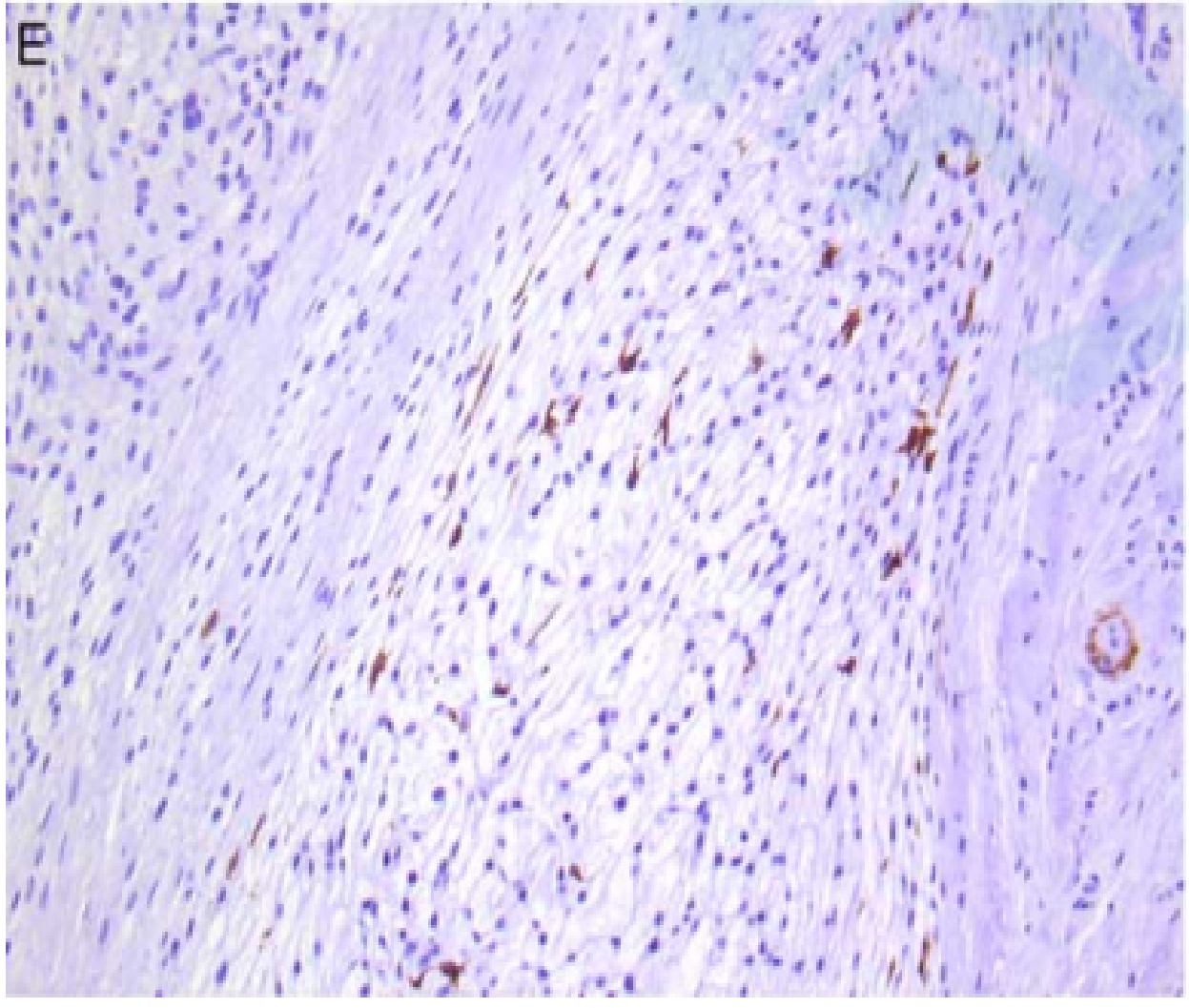
Keratin (AE1/AE3)



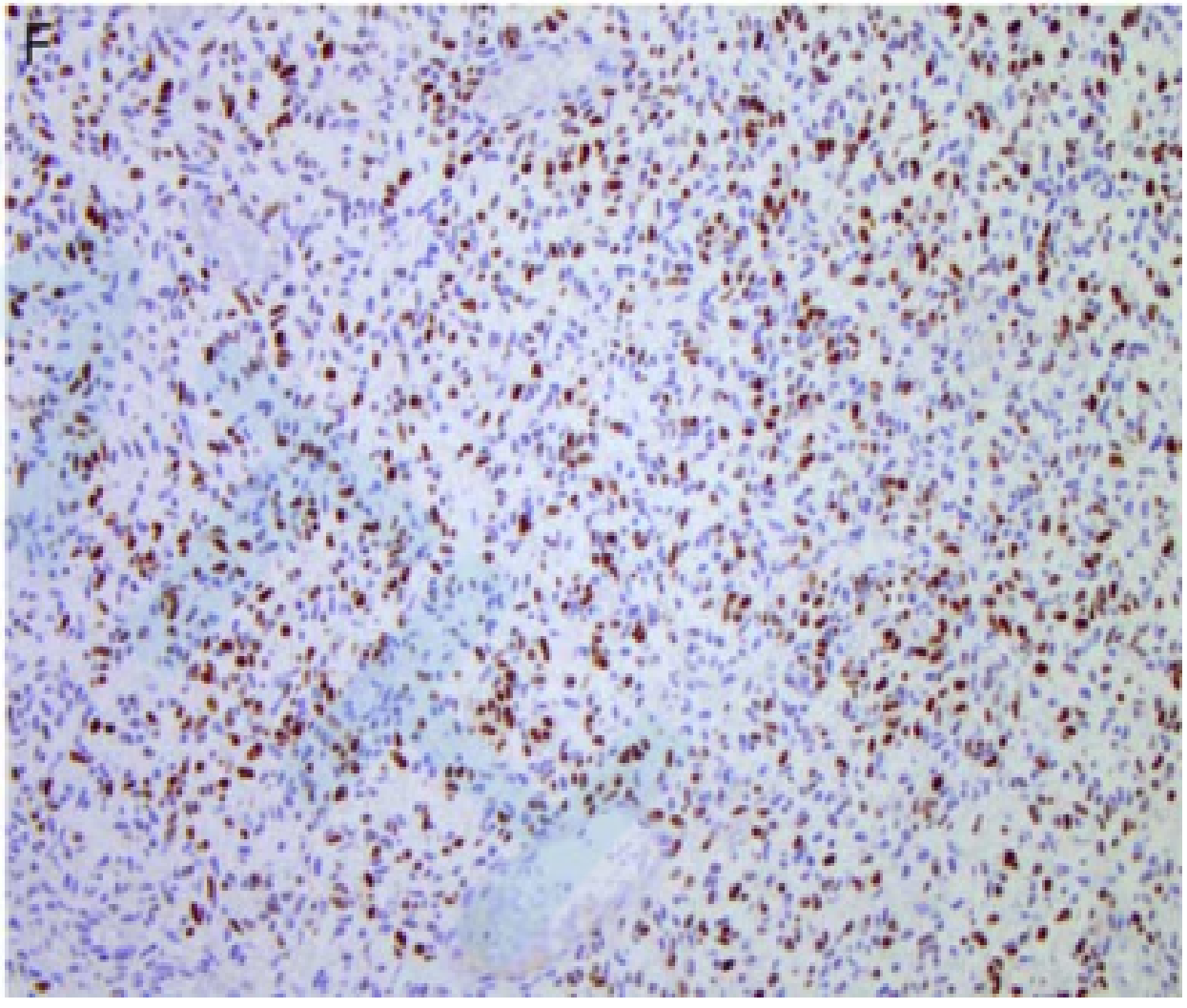
desmin



SMA



myogenin



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3	5+	5+	1+	1+	–	3+	RNA-Seq	*RREB1-MKL2*
4	4+	3+	1+	–	–	1+	RNA-Seq	Negative
5	NP	NP	NP	NP	NP	NP	RNA-Seq	*RREB1-MKL2*
6	5+	5+	2+	1+	2+	2+	RNA-Seq	*RREB1-MKL2*
7	5+	2+	–	NP	NP	–	RNA-Seq	*RREB1-MKL2*
8	5+	3+	–	NP	NP	NP	RNA-Seq	*RREB1-MKL2*
9	1+	3+	–	–	–	3+	RNA-Seq	*RREB1-MKL2*
10	2+	3+	–	–	–	3+	RNA-Seq and FISH	*RREB1-MKL2*
11	5+	3+	2+	4+	–	2+	RNA-Seq	*RREB1-MKL2*
12	4+	2+	1+	1+	–	NP	FISH	*RREB1-MKL2*
13	5+	2+	1+	1+	–	NP	FISH	*RREB1-MKL2*
14	4+	1+	–	1+	–	NP	FISH	*RREB1-MKL2*
15	4+	NP	–	NP	–	NP	FISH	*RREB1-MKL2*
16	4+	1+	–	–	–	NP	FISH	*RREB1-MKL2*
17	2+	NP	–	NP	–	NP	FISH	*RREB1-MKL2*
18	5+	5+	2+	1+	–	3+	FISH	*RREB1-MKL2*
19	5+	2+	2+	1+	–	NP	FISH	*RREB1-MKL2*
20	4+	1+	1+	3+	1+	3+	FISH	*RREB1-MKL2*
21	5+	2+	2+	–	–	–	FISH	*RREB1-MKL2*

– indicates negative; GFAP, glial fibrillary acid protein; NP, not performed; SMA, smooth muscle actin.

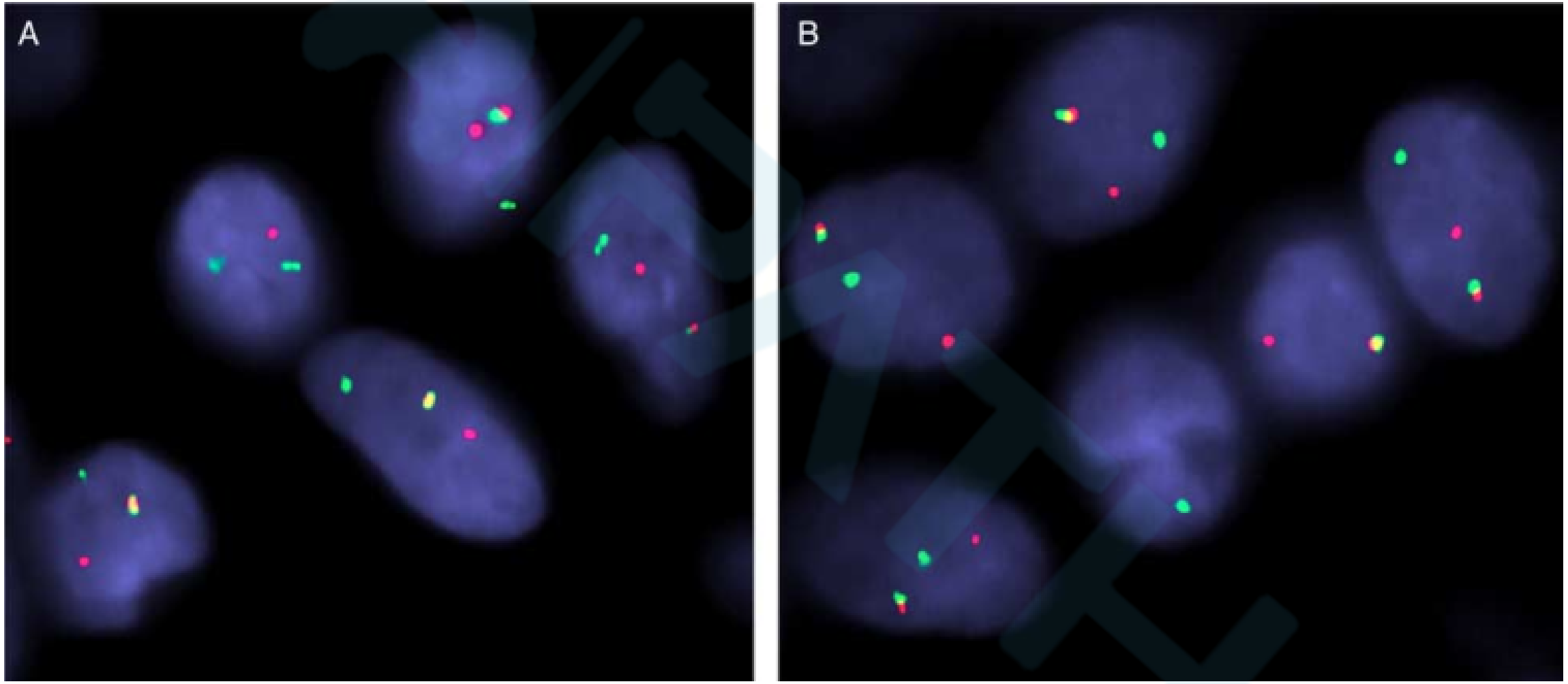


FIGURE 4. Representative FISH in ectomesenchymal chondromyxoid tumor (patient 20). Rearrangement of: *MKL2* (A) and *RREB1* (B) (both images: red, centromeric; green, telomeric).

04

DISCUSSION

讨　论

DISCUSSION

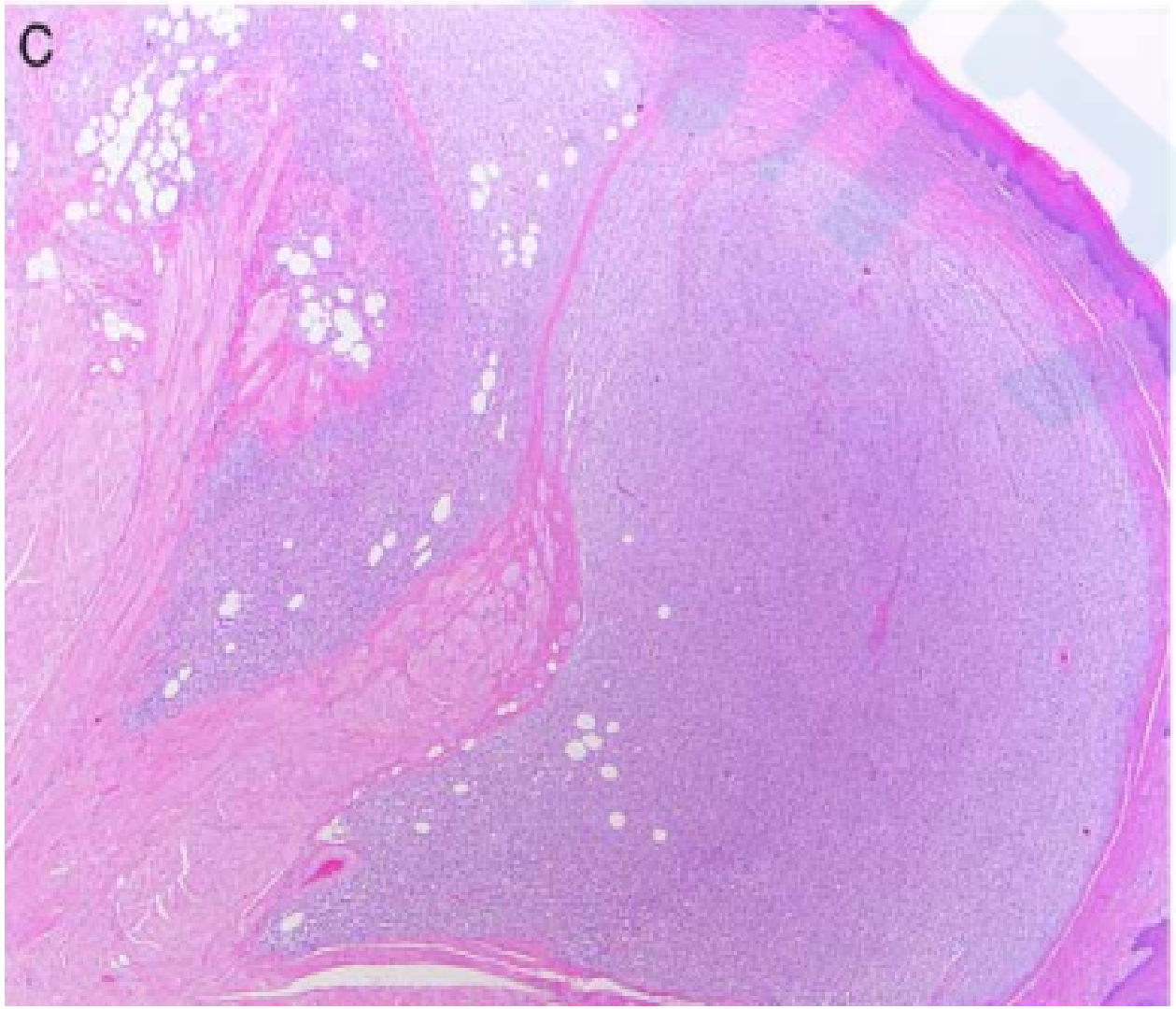
- 在本研究中，患者年龄范围较宽（13-59y），具有轻微的女性偏好，且所有病例均起源于舌背部，这与以往的报道类似。
- 我们的所有病例病变都位于舌，实际上，所有的先前报道的真正的病例都发生于此，有2例报道发生于硬腭的病例，一例先前已经有学者质疑，另一例也缺乏ECT的典型形态和免疫表型。
- 尽管在本系列病例中有几例手术切缘查见病变组织，但仅有一例局部复发，无转移。证实了临床上的良性生物学行为。

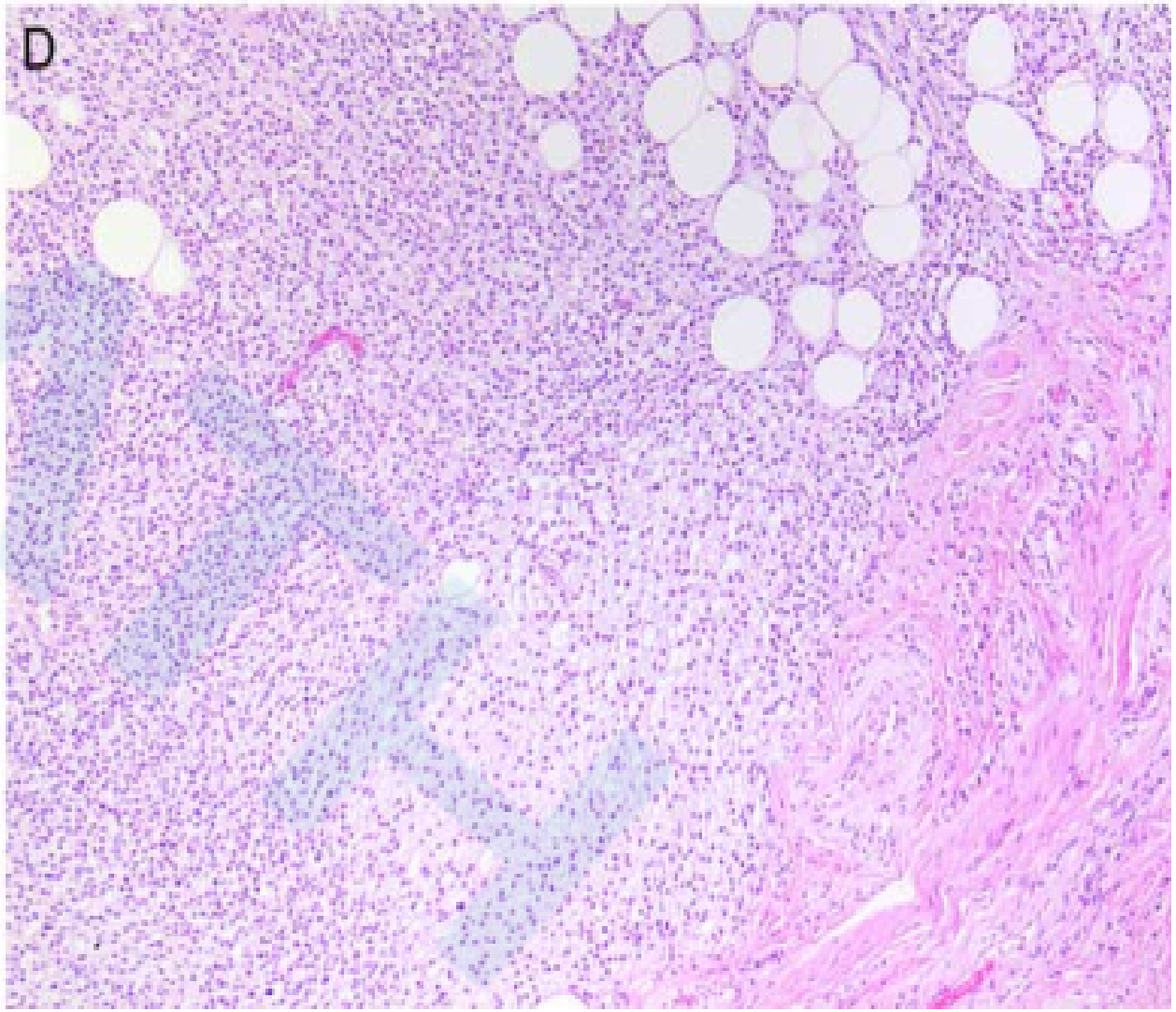
DISCUSSION

- ECT具有独特的形态和免疫表型，与先前的报道相似， 尽管关于Desmin的表达具有争议，但我们的结果显示它的表达尽管局灶，但很普遍（10/16）。

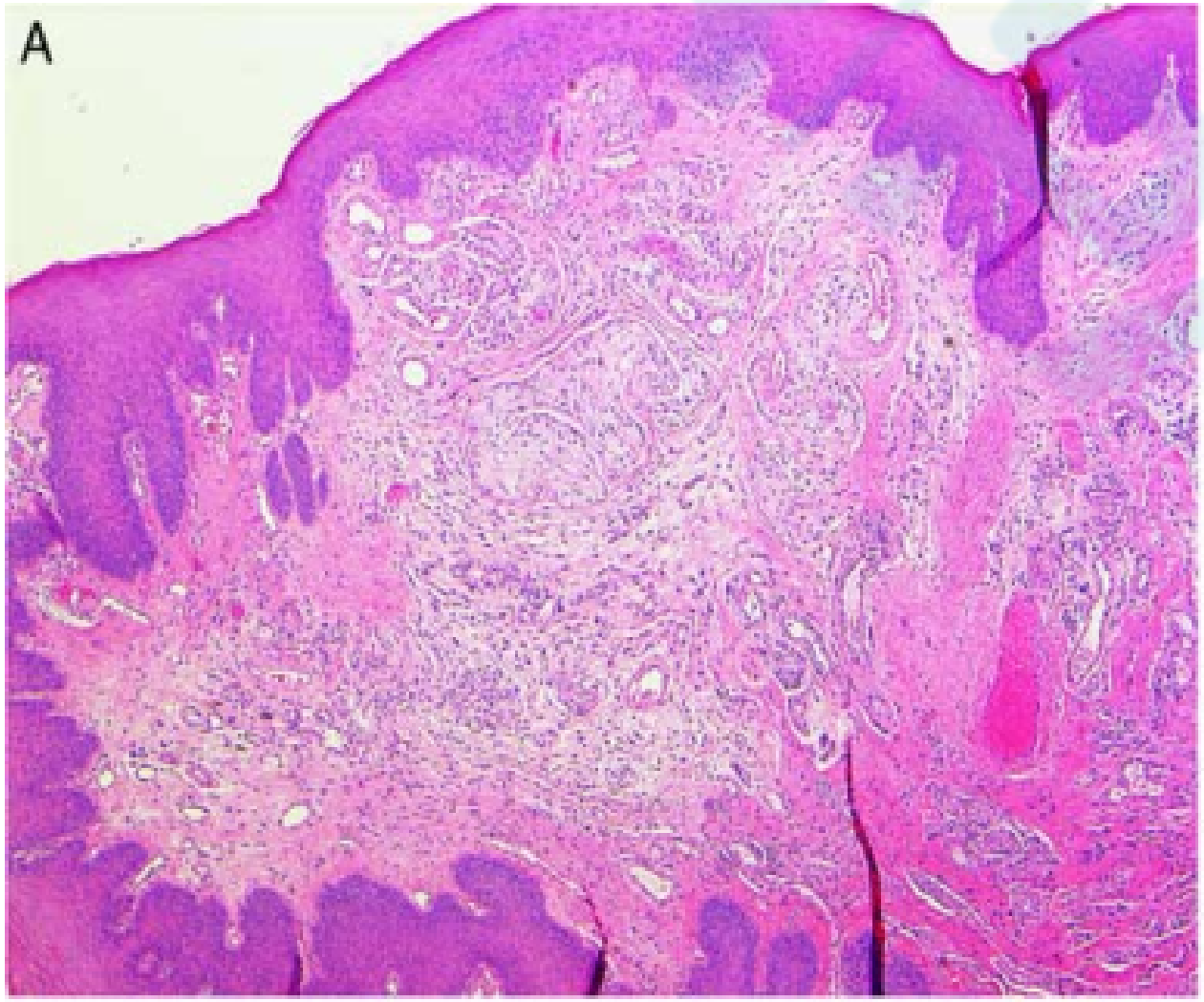
- 在本研究的首发病例中发现了RREB1-MKL2融合基因后，使用了RNA-Seq和FISH的组合证实了该融合产物存在于21例病例中的19例，而缺乏RREB1-MKL2融合的2例不具有ECT的特征性形态。其中1例未发现任何基因融合，另一例检测到EWSR1-CREM的融合。

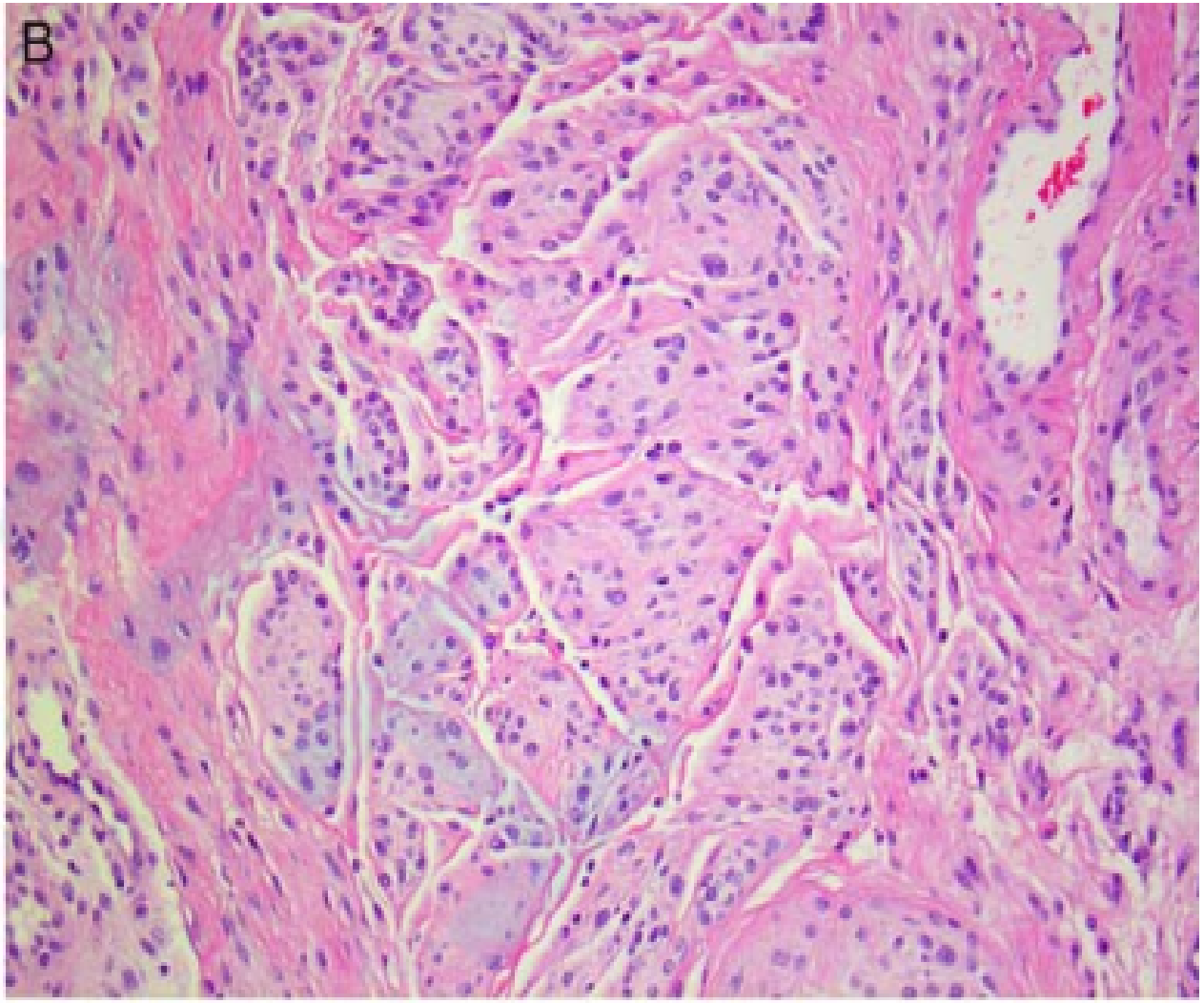
Case 4：lacking any gene fusions by RNA-Seq





Case 2：EWSR1-CREM Fusion





DISCUSSION

Histopathology 2016, **69**, 607–613. DOI: 10.1111/his.12973

A subset of ectomesenchymal chondromyxoid tumours of the tongue show *EWSR1* rearrangements and are genetically linked to soft tissue myoepithelial neoplasms: a study of 11 cases

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在27%（ 3/11 ）ECT病例中发现EWSR1重排

本文的研究中，具有EWSR1-CREM融合的病例，与先前报道的有EWSR1重排的ECT病例在形态学上类似，作者认为这些病例可能更适合归入伴有EWSR1-CREB家族基因融合的黏液样间质肿瘤。但对于这一类肿瘤的研究文献有限，目前难以做出有意义的推论。

DISCUSSION

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RESEARCH ARTICLE

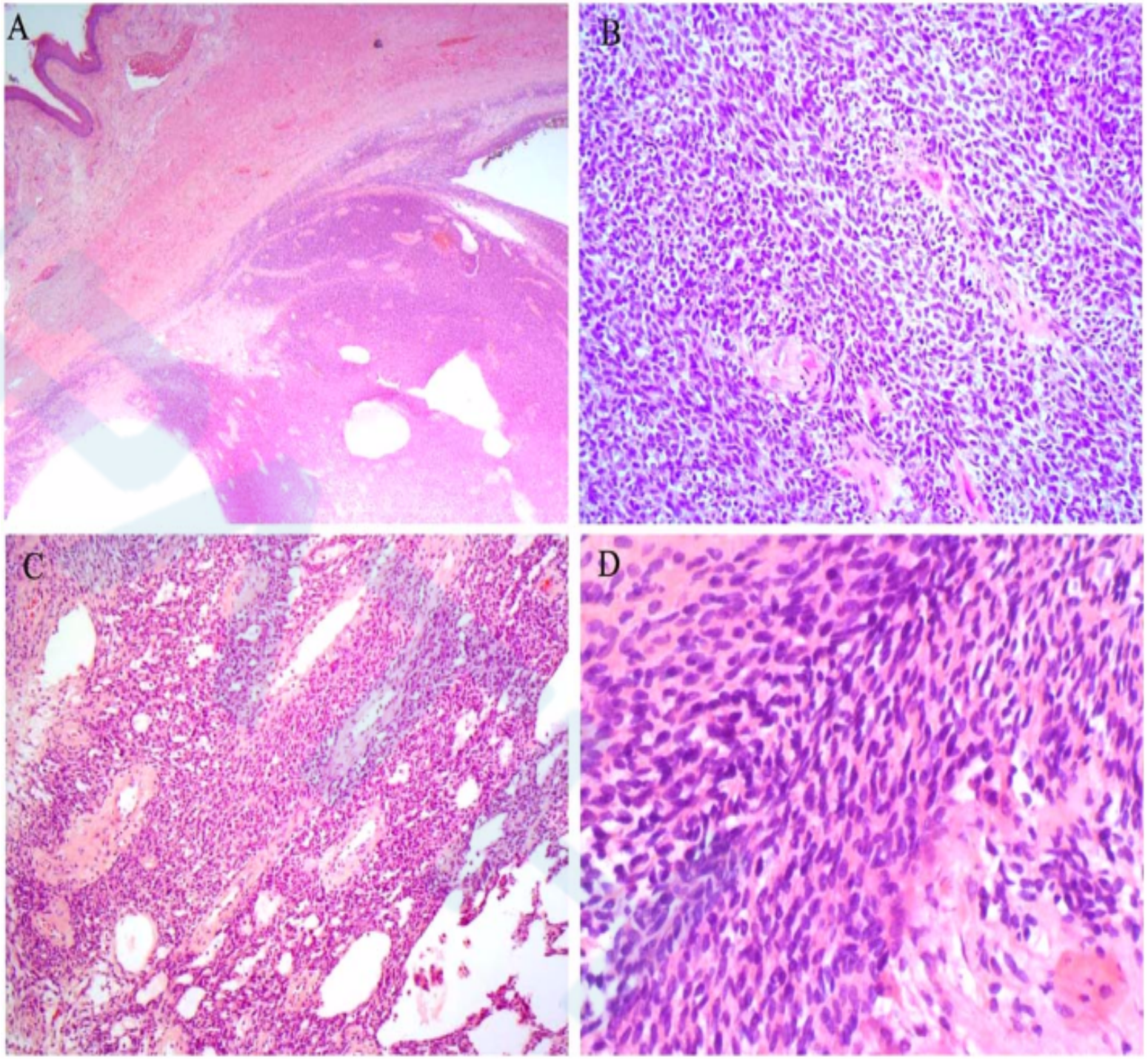
WILEY

RREB1–MKL2 fusion in biphenotypic "oropharyngeal" sarcoma: New entity or part of the spectrum of biphenotypic sinonasal sarcomas?

Aurore Siegfried[1,2] | Claire Romary[3] | Fréderic Escudié[1] | Yvan Nicaise[1] | David Grand[1] | Philippe Rochaix[2,3] | Béatrice Barres[1] | Sébastien Vergez[4] | Christine Chevreau[5] | Jean-Michel Coindre[6,7,8] | Emmanuelle Uro-Coste[1,2] | Sophie Le Guellec[2,3]

DISCUSSION

- 大体及组织学特征：3.5cm的咽旁肿块，由梭形、卵圆形细胞束状排列组成，胞核均匀，核分裂罕见，偶见囊腔形成。
- 免疫组化： S-100 、SMA、desmin和myogenin斑片状阳性表达
- 分子病理：通过RNA-Seq检测到RREB1-MKL2基因融合



作者考虑双表型口咽肉瘤是否是非典型ECT的例子，或是RREB1-MKL2是具有多效性的融合基因，类似于EWSR1-ATF1在透明细胞肉瘤、血管样纤维组织细胞瘤及唾液腺透明细胞癌中的关系。但目前尚无此类研究。

DISCUSSION

关于外胚间叶软骨黏液瘤的组织发生目前还一直处在争论当中，但也有一些猜测：
1.来源于神经嵴的未分化的外胚间充质干细胞；
2.来源于小唾液腺或软组织的肌上皮源性肿瘤；
3.肿瘤细胞的形态类似于神经元，可能表现出与未分化胚胎干细胞相似的多向分化特征等

MKL2编码Myocardin 2-a血清反应因子的转录共激活因子，参与了平滑肌和骨骼肌分化以及神经元发育。RREB1-MKL2的融合基因使MKL2表达增加，从而调控神经和肌源性分化。

鉴于本研究中的分子发现，结合ECT独特的临床和组织病理学特征，提示其可能代表一种独特的肿瘤。第一种猜想目前更具可能性。

总结：

01

01.本研究为迄今最大数量的外胚间叶软骨黏液瘤。

02

02.证实了ECT对于舌背部的强烈偏好

03

03.扩大了肿瘤的形态学及免疫组化谱

04

04.发现了RREB1-MKL2是外胚间叶软骨黏液瘤的特征性基因融合。

谢谢聆听

Thank you for listening.