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EWSR1-SMAD3–rearranged Fibroblastic Tumor

An Emerging Entity in an Increasingly More Complex Group of Fibroblastic/Myofibroblastic Neoplasms

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指导老师：徐玉乔

纤维母细胞/肌纤维母细胞性肿瘤（Fibroblastic/Myofibroblastic Neoplasms）

- 形态上既有纤维母细胞的特点，又具有肌纤维母细胞的某些特点，占间叶组织肿瘤的绝大多数。
- 这2种细胞可能是单一类型细胞的不同功能状态。
- 这些细胞在不同的病例中，甚至同一病例的不同时相也存在差异。

EWSR1（ The Ewing sarcoma breakpoint region 1 ）

- EWSR1，又叫尤文氏肉瘤断点区域1 。
- 是一个高度混杂的基因，在许多不同的肿瘤类型中发生重排。

研究背景

研究背景

- 仍然存在很多未被精确分类的软组织肿瘤
- 软组织肿瘤组织学形态类似，很难进行区分
- Kao等通过NGS报道了3例新型肢端成纤维细胞复发性肿瘤，均存在EWSR1-SMAD3基因融合

EWSR1-SMAD3基因融合的纤维母细胞瘤（ESFT）

用免疫组织化学(包含IHC)，荧光原位杂交(FISH)和NGS 辅助技术，作者找到了4例与最近报告的病例具有非常相似的组织学特征的病例。将这类病例命名为EWSR1-SMAD3基因融合的纤维母细胞瘤（ESFT）。

目的

目的（一）	目的（二）
追加4例新型病例，命名为ESFT，并研究它的鉴别诊断；	ERG是EFST的特异性标记，分析类似肿瘤ERG的表达情况。

材料&方法

TABLE 1. Clinical, Immunohistochemical, and Molecular Genetic Features

Case	Sex/ Age (y)	Location	Duration	Size (cm)	FISH	NGS	IHC +	IHC −	Recurrence	Length of FU (y)	Original Diagnosis	Comment
1	F/5 and 15	Hand—palm	3 y	1.2 and 0.3	NA	*EWSR1-SMAD3*	ERG in both; focal SAT-B2 staining in the 2nd tumor, negative in the first tumor	SOX-10; S100; EMA; CD34; SMA; Actin E; Desmin; SAT-B2; OSCAR; Pan-TRK; SAT-B2	Yes in 10 y	18	Unusual lipofibroma-tosis	Incomplete excision in both the original tumor and the reexcision
2	F/68	Interphalangeal joint of the thumb	10 months	1.5×0.7×0.5	NA	*EWSR1-SMAD3*	ERG, focal SAT-B2 staining	SOX-10; S100; CD34; EMA; Desmin; OSCAR; HMB45	No	10	Unusual fibromatosis	Incomplete excision but no recurrence
3	F/39	Calf	NA	1×0.5×0,5	NA	NA	ERG	S100; EMA; CD34; SMA; Desmin; OSCAR; AE1/3 Synaptophysin; Chromogranin; CD117; DOG-1	No	7	Benign plexiform spindle cell tumor	Early reexcision —no additional tumor tissue
4	F/34	Left foot—dorsal metatarsal aspect	NA	1.1×0.8×0.5	Positive	*EWSR1-SMAD3*	ERG	SOX-10; S100; EMA; CD34; SMA; Desmin; Caldesmon; AE1/3; Beta Catenin; MUC4	Recent case	Recent	Unusual myofibroma	Slowly enlarging, painful, no history of trauma

F indicates female; FU, follow-up; NA, not available.

材料&方法

患者年龄：5-68岁，女性，年龄中位数是16.5

发生部位：四肢皮下软组织

2例发生于手 部，1例发生于脚部，1例发生于小腿部

肿瘤大小：1-1.5cm，中位数1.2cm

预后：最近1例病例除外，随访：7-18年，中位数是11.7，1例病例10年后复发。

材料&方法

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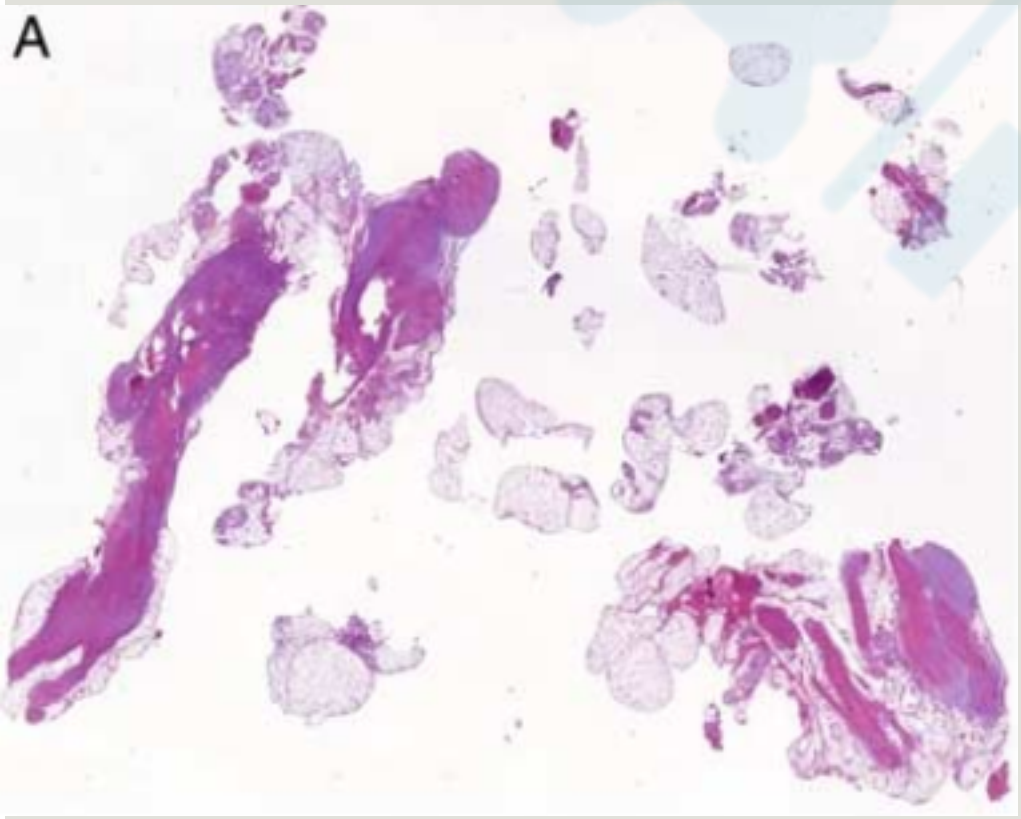
结果：ESFT形态



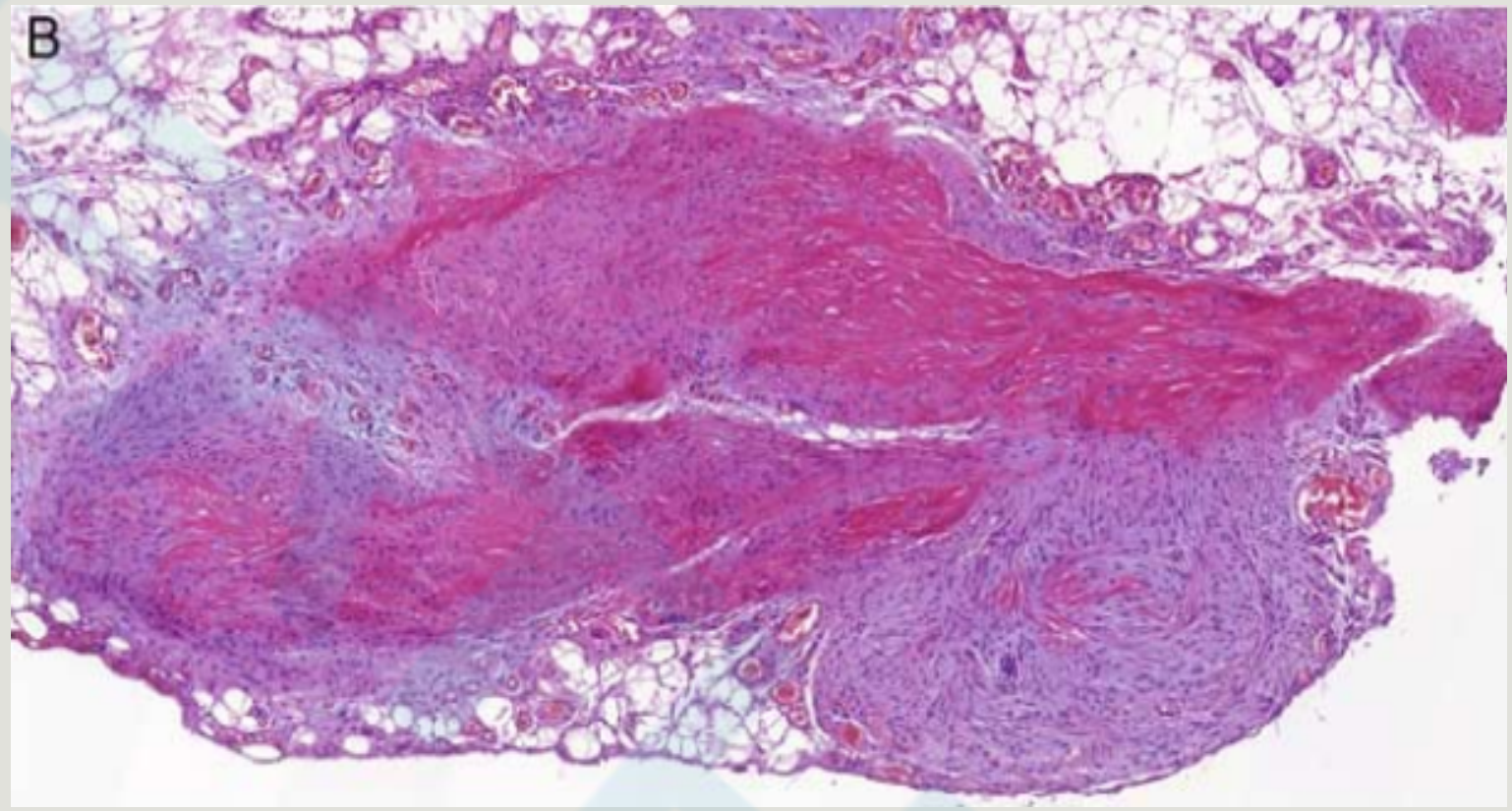


FIGURE 1. The original tumor in case 1 was vaguely lobulated or plexiform (A). It showed a distinct zonation pattern with central hyalinization and the spindle cell component located at the periphery, engulfing a small amount of the surrounding subcutaneous adipose tissue (B, C). Higher power view of the bland spindled cells with elongated, focally wavy nuclei growing in relatively hypercellular and well-organized fascicles of intermediate length that frequently intersected with each other at different angles (D). The recurrence created a single tumorous nodule (E), engulfing a small amount of the surrounding fat and showing the characteristic hyalinization (F).

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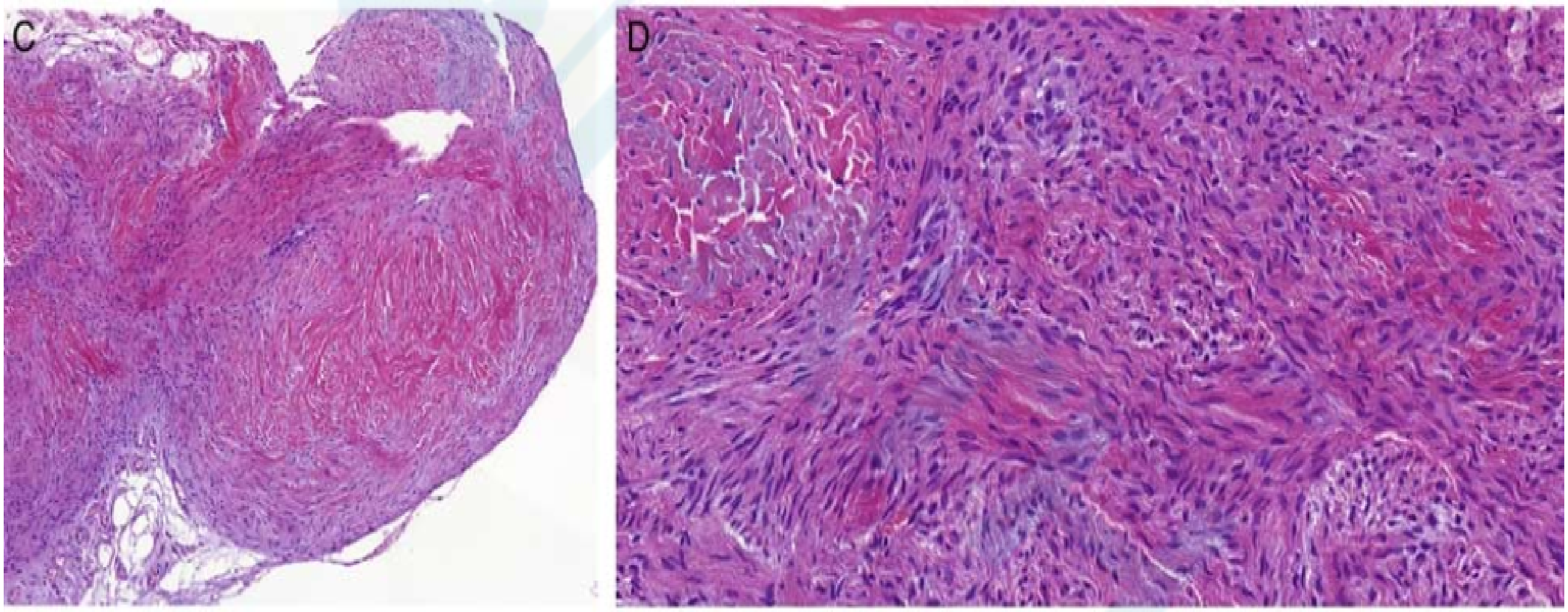

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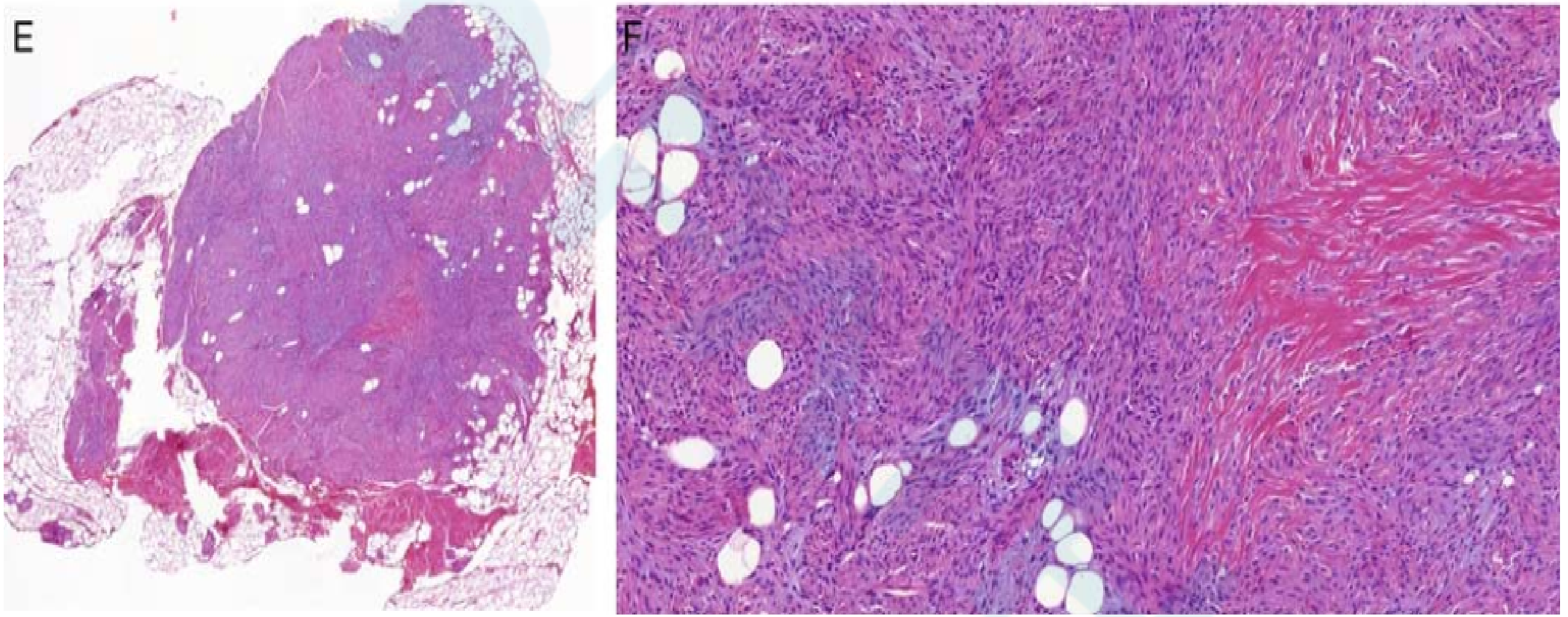

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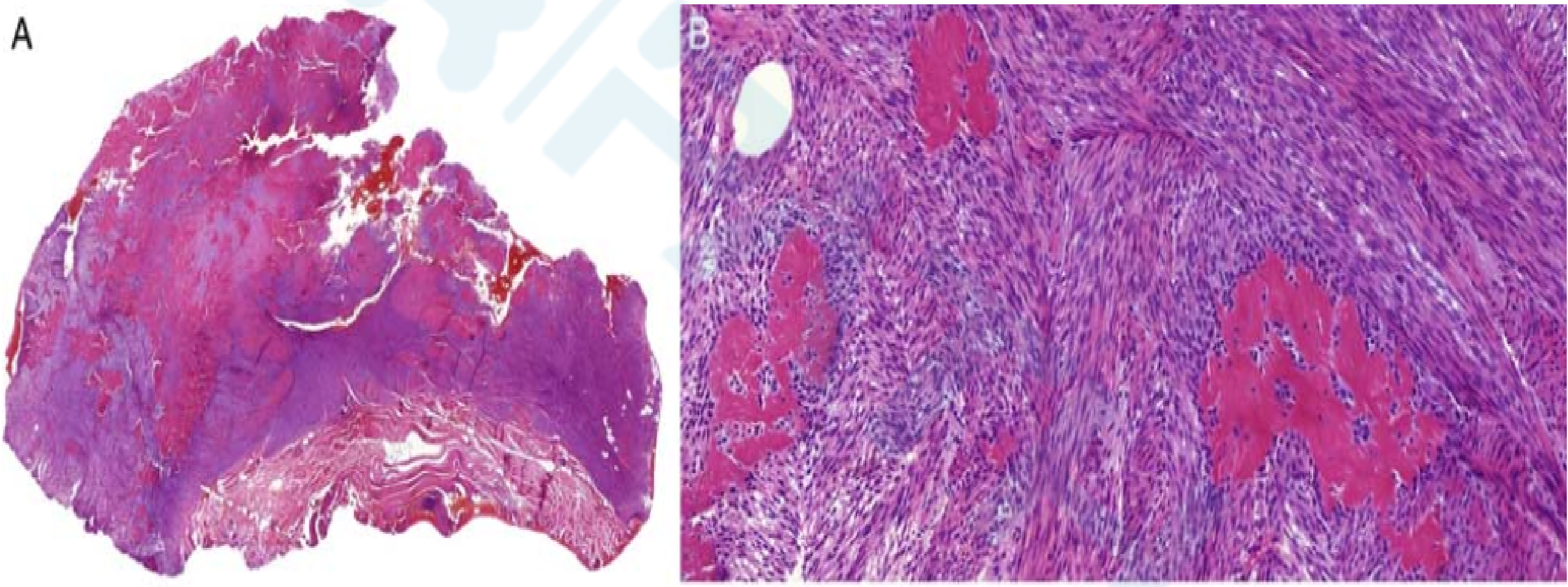

FIGURE 2. The tumor in case 2 created a single tumorous nodule. A small amount of engulfed adipose tissue is seen on the right (A). The hypercellular fascicles frequently intersected with each other at different angles, and in this case, randomly intermingled with the hyalinized component (B). High power view of the prominently hyalinized component that lacked calcifications with only a few viable spindled cells (C). The bland spindled cell component with elongated, focally wavy nuclei, which were round when observed on cross-section and did not show conspicuous nucleoli (D). Strong nuclear staining with ERG (E). This tumor also showed focal weak to moderate nuclear staining with SAT-B2 (F).

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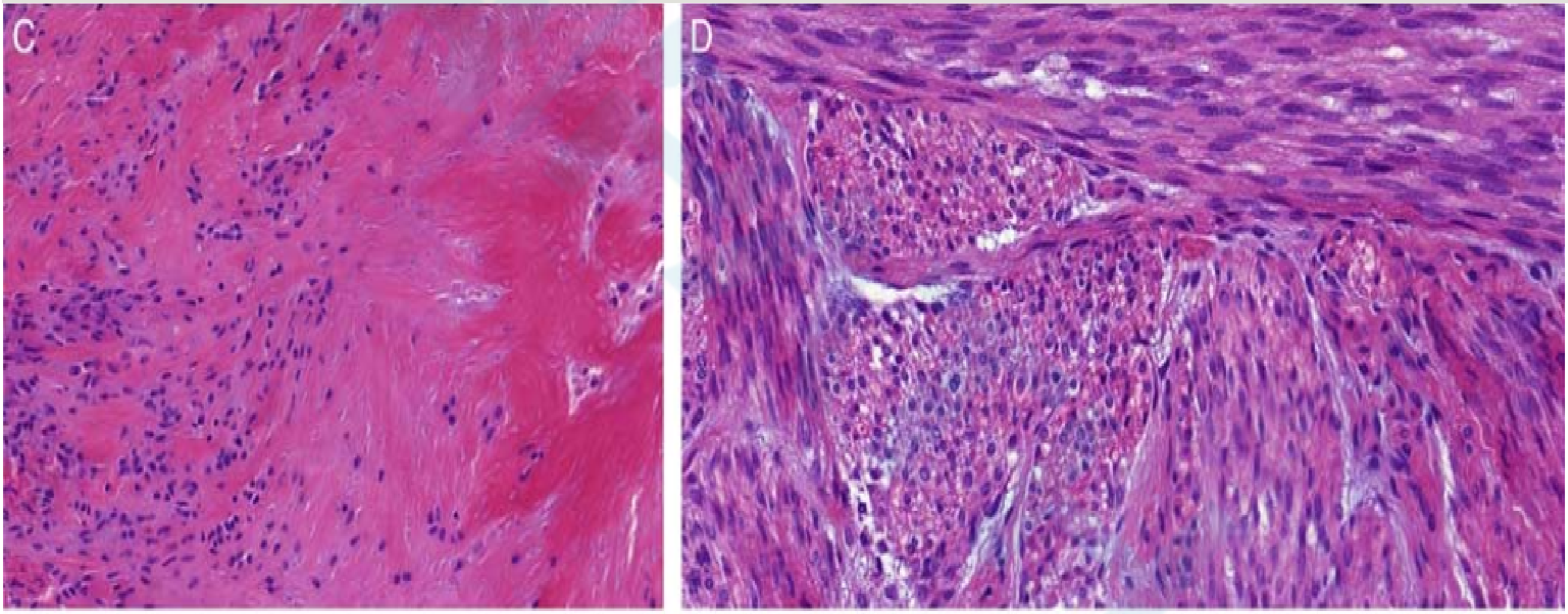

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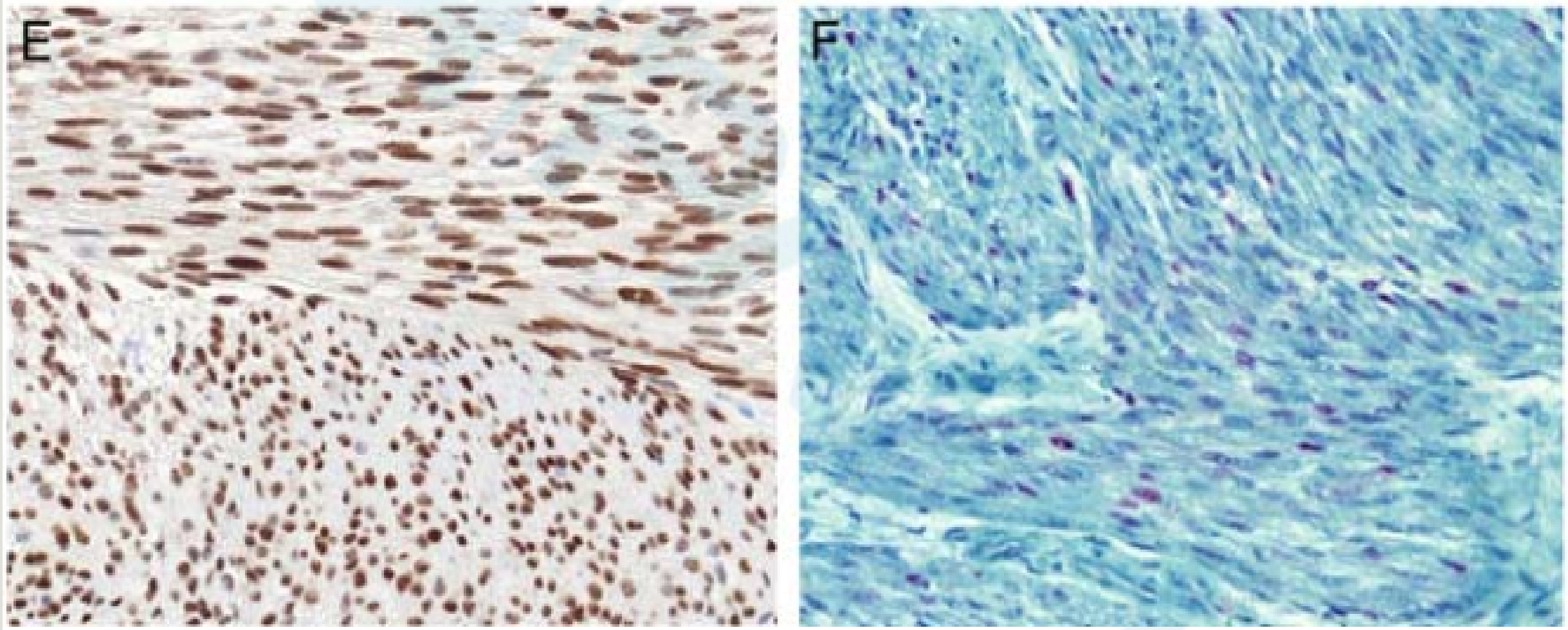
结果：IHC ESFT



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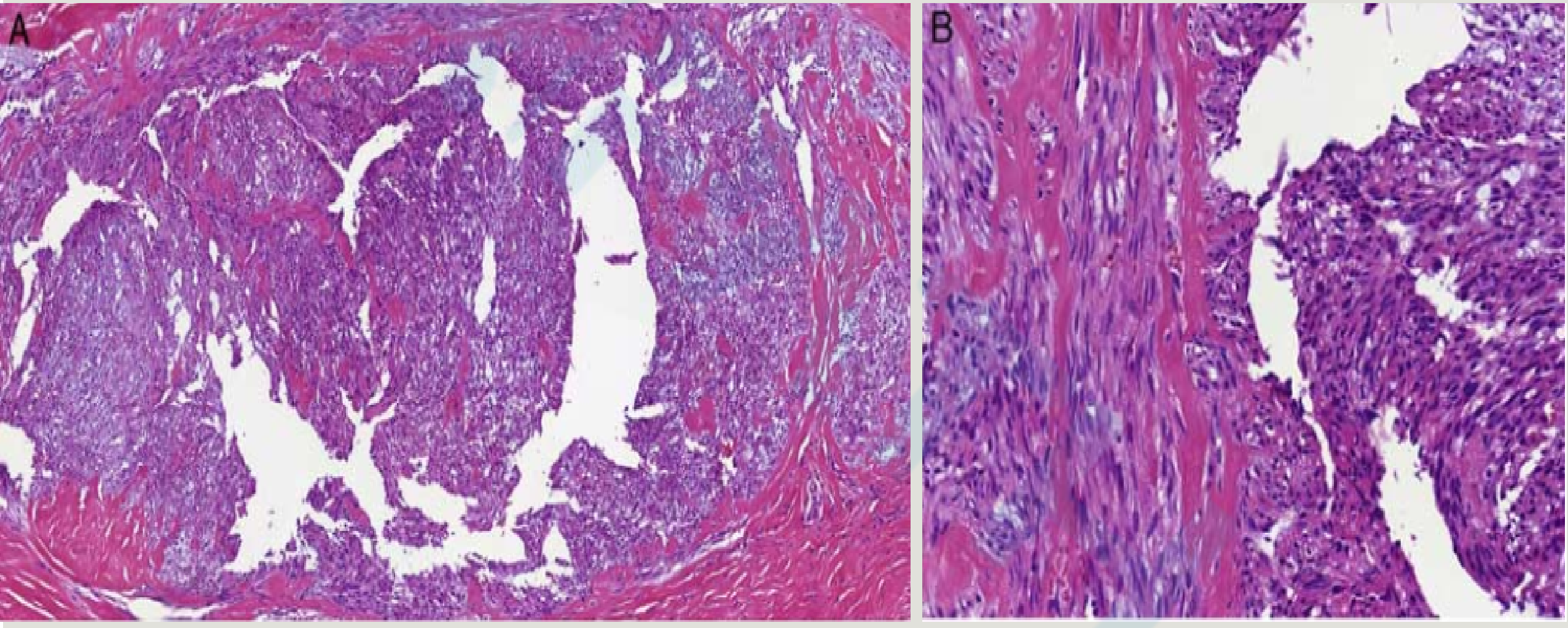

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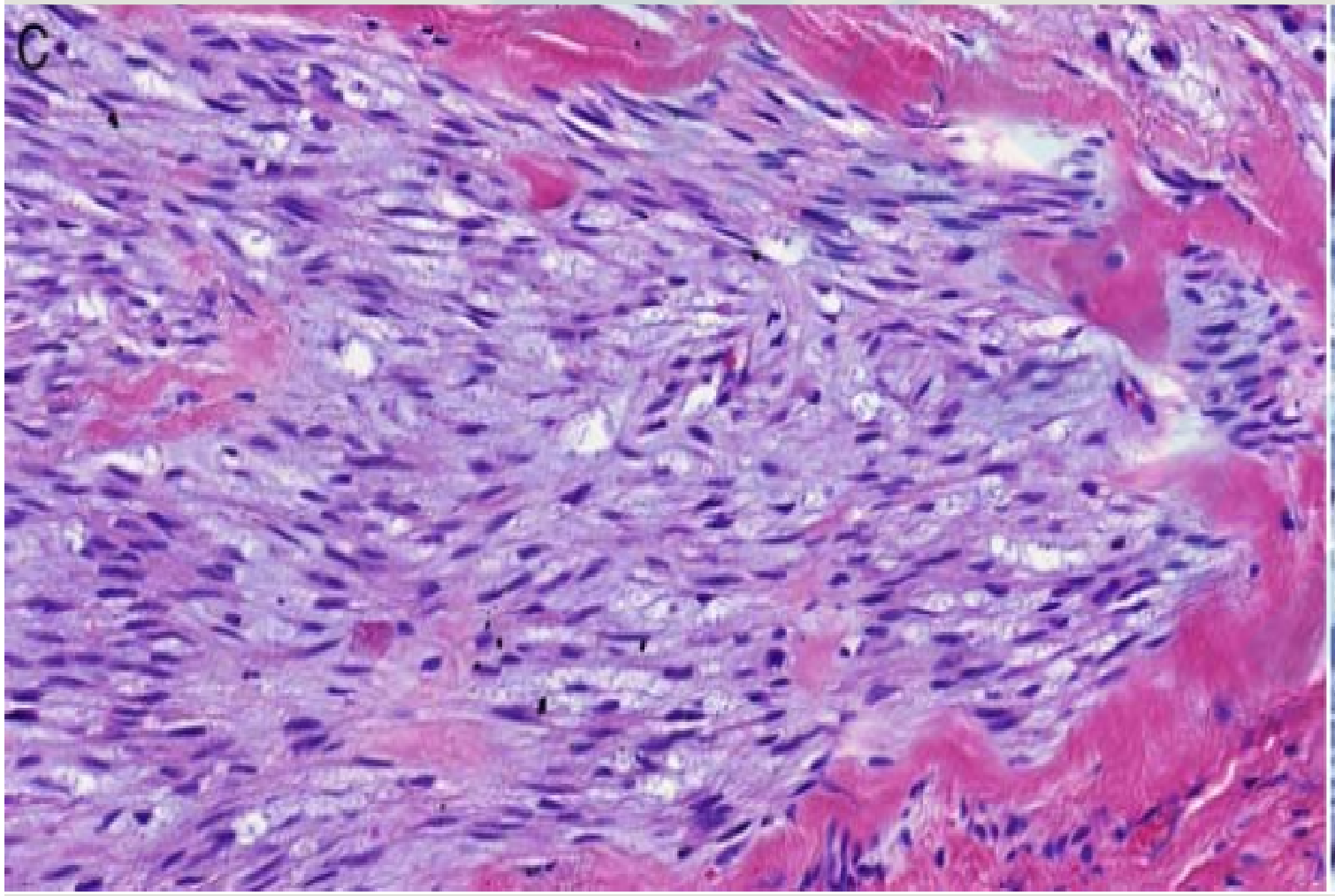

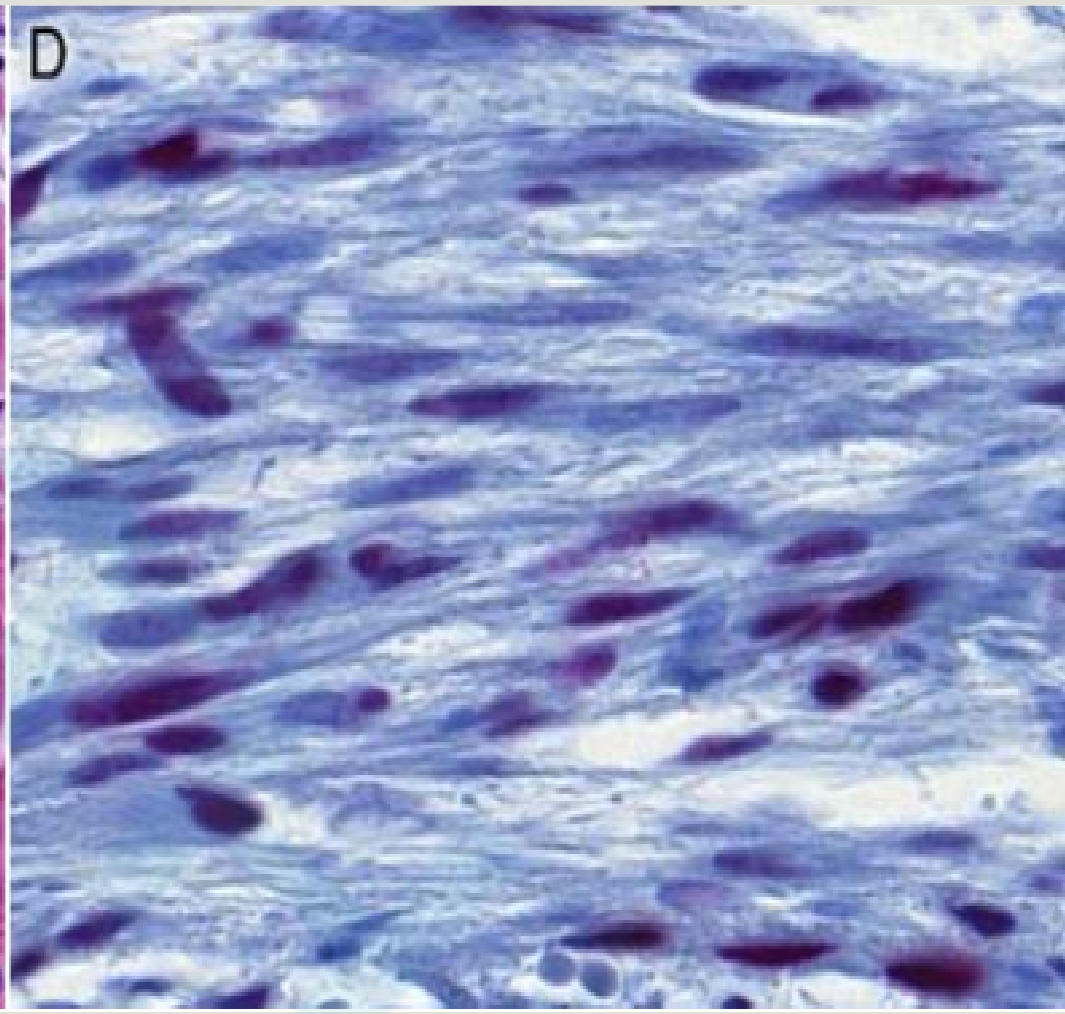

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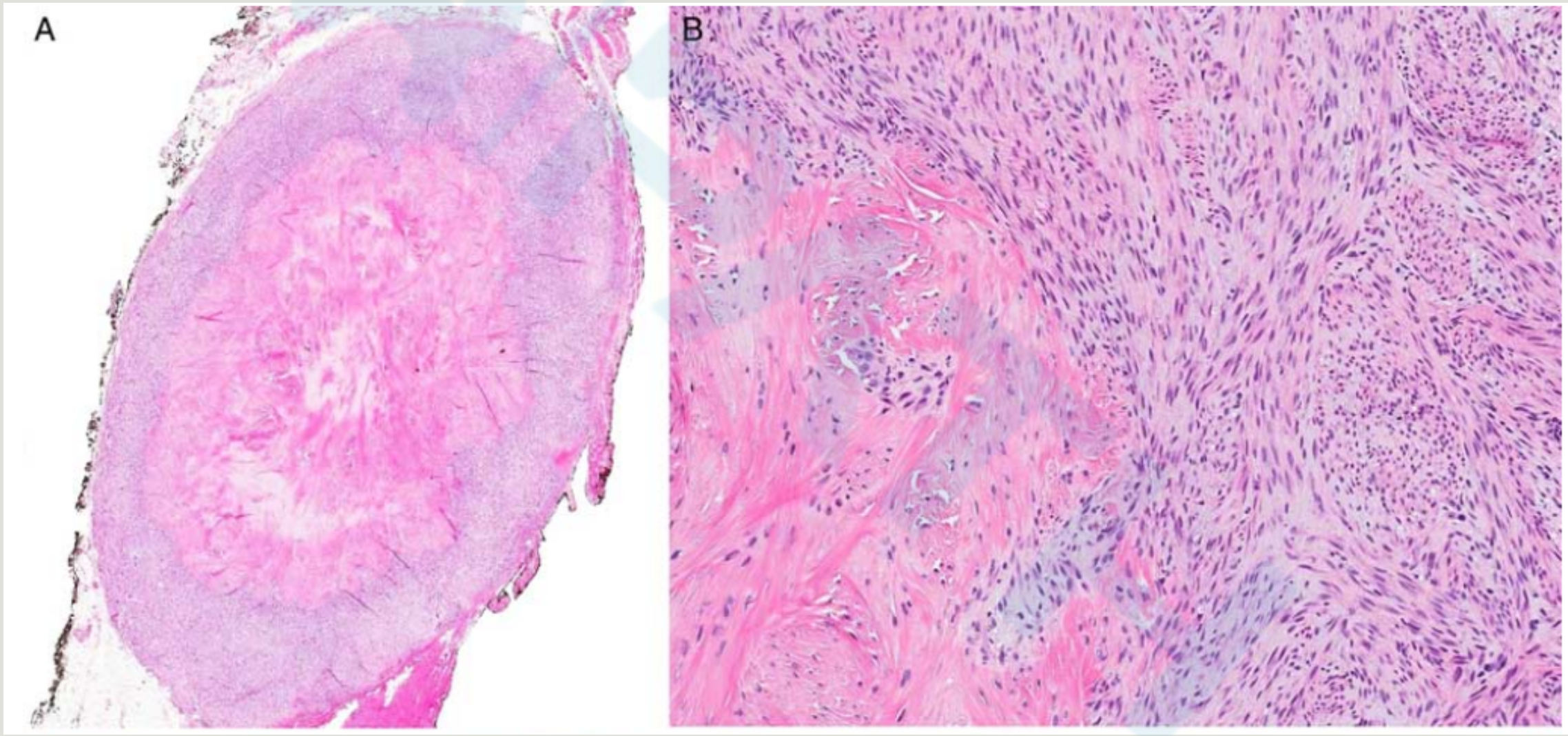
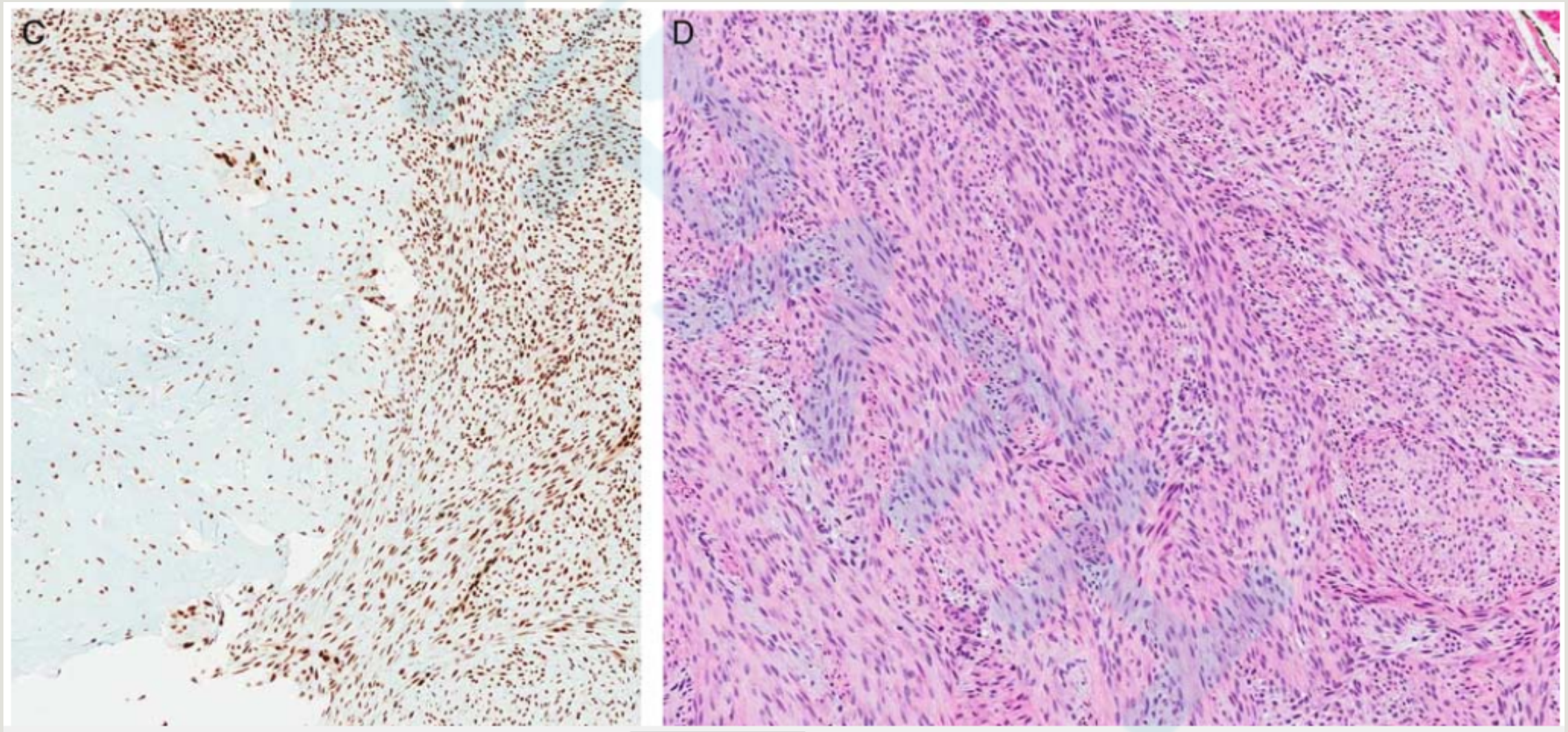


FIGURE 4. The tumor in case 4 created a single tumorous nodule which featured a distinct zonation pattern with the spindle cell component located at the periphery and central hyalinization (A). The prominently hyalinized component gradually merged with the more peripherally located spindle cell proliferation (B). Strong nuclear staining with ERG (C). Pleomorphism, atypia or mitoses were absent in the spindled cell component (D).

结果：ESFT形态



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讨论

- 成纤维细胞/肌成纤维细胞性肿瘤包含许多肿瘤类型，他们在形态学和免疫组化表达上都有重叠，对诊断造成困难。

- NGS能够发现这类肿瘤的分子水平的特点，对复杂病例的诊断提供帮助。并且能够将潜在的新的成纤维细胞肿瘤区分开。

- 之前有学者报道了一种新型的梭形细胞肿瘤，存在EWSR1-SMAD3基因融合。结合本文的病例，一共7例病例。相对于之前的3例病例，作者发现了一些新的特征，还需对更多病人进行观察，得出一些总体的观察结论。

讨论1：EFST的临床特点

- **发生部位**：结合以前的文献报道的3例病例，一共7例病例。前3例病例都发生于下肢肢端，本文病例中1例发生于足背，2例发生于手掌端，1例发生于小腿，所以并不是都发生于肢端。
- EFRT多发生于女性（6/7）。
- **好发年龄**：分布年龄范围广泛，有的出现在婴儿或儿童身上，也有近70的老年人 。
- **生长方式**：浸润性生长，易局部复发。
- **预后**：5例病例中3例在5个月-10年复发，2例采取积极手术，未复发。

讨论2：ESFT形态学特点

- 显微镜下观察，低倍镜下，细胞呈结节状排列，肿瘤呈模糊的小叶状或丛状，向周围组织浸润。具有2种主要成分：

- 1，交叉排列，密度高，呈簇状的梭性细胞；

- 2，有相似的细胞组成和结构，但可见玻璃样变，并且存在少量增殖旺盛的细胞（之前的病例中，这个区域还存在局灶的钙化）。

- 两种成分呈明显的分带，中间为玻璃样变的成分，梭形细胞位于周围。

讨论3：EFST IHC

- 所有的EFST病例，**ERG均显示核的强阳性**。
- 在之前文献报道的病例中，有1例病例角蛋白和EMA表达不明确。
- 在本文的病例中，有2例当前的病例和1例复发病例，STAB2显示局灶核的弱阳性和中等阳性染色。

讨论5：ESFT鉴别诊断

- ✓LPF 脂肪纤维瘤病
- ✓CAF 钙化性腱膜纤维瘤
- ✓MF 肌纤维瘤/肌纤维瘤病
- ✓Infantile digital fibroma/fibromatosis婴儿指/趾纤维瘤病
- ✓Palmar/plantar fibromatosis 掌/足底纤维瘤病
- ✓MSS 单相滑膜肉瘤

讨论5：LPF（Lipofibromatosis ）

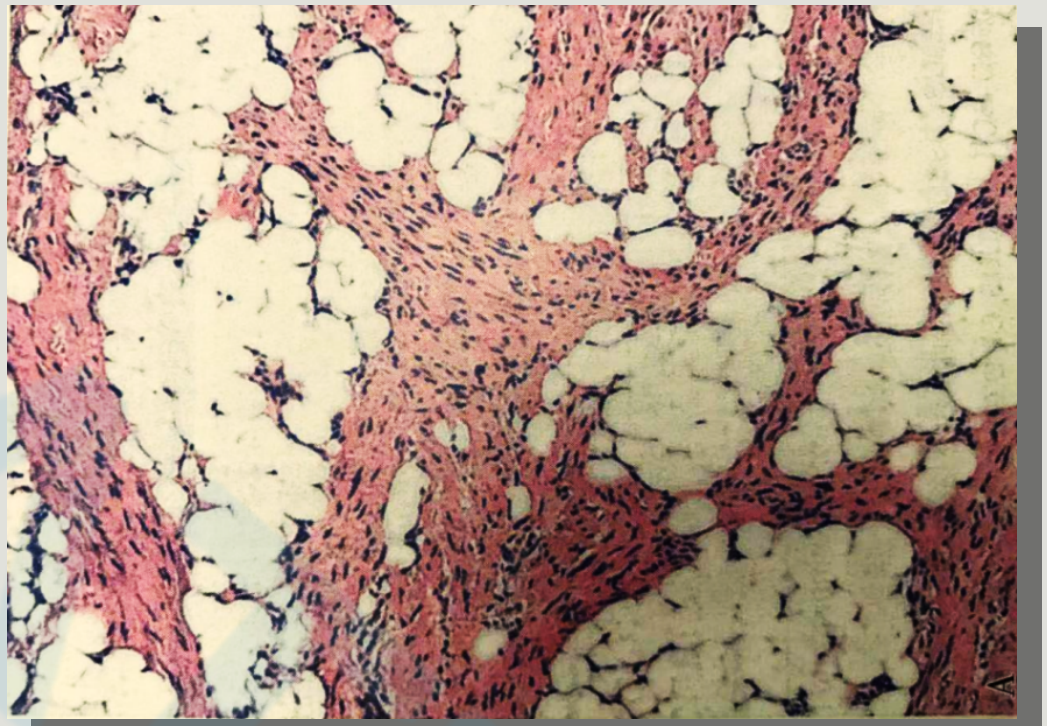
脂肪纤维瘤病 (LPF)

好发人群：只发生与儿童

（婴儿~ > 10岁儿童 ）

ICD-O 编码：8821/1

发生部位：手足部



组织病理学：肿瘤含有交错分布的条纹状成熟脂肪组织和纤维性梭形细胞成分，后者主要位于脂肪组织间隔处。主要特点是保留有脂肪结构并缺乏实性纤维性增生。

免疫表型：梭形细胞CD34、bcl-2、S-100、EMA局灶阳性

讨论5：ESFT VS LPF

- LPF是一种罕见的小儿间质瘤,多发于手部和脚部。 ESFT经常浸润周围的 脂肪组织,因此可能被误认为是LPF。
- LPF无明显玻璃样变区域；
- LPF细胞束未呈现明显的交叉模式；
- LPF细胞呈卵圆形而不是梭形；
- LPF脂肪成分较多,通常表现在整个肿瘤上。相比之下,ESFT的脂肪成分有限,通常只在肿瘤的边缘；
- LPF CD34（+）,大约1/3的病例中表达为S-100。

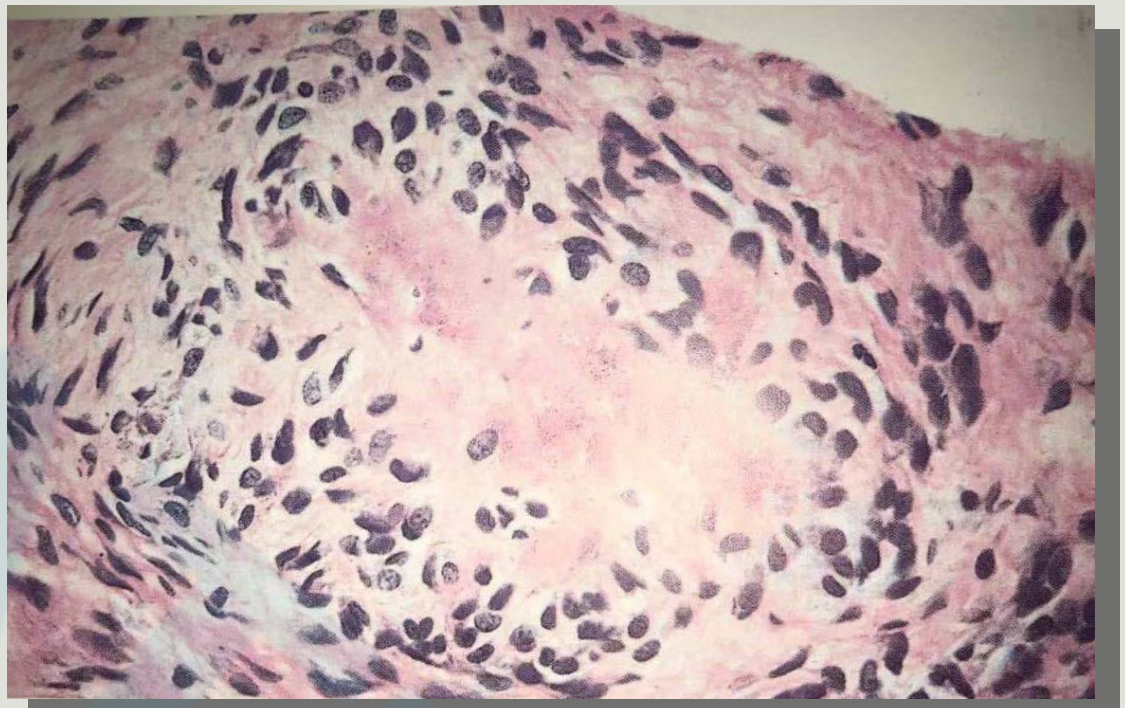
讨论5： Calcifyingaponeurotic fibroma（CAF）

钙化性腱膜纤维瘤(CAF)

好发人群：患者年龄0-64岁

平均年龄12岁

男性略多见



ICD-O编码：8810/0

发生部位：手掌、足底、腕部和踝部

组织学特点：（1）结节性钙化灶；（2）融合的钙化结节之间为细胞成分稀少的梭形纤维母细胞性细胞，并浸润周围软组织。

免疫组化：只有有限病例经过免疫组化的检测，不同程度表达波纹蛋白、SMA、MSA、CD99和S-100

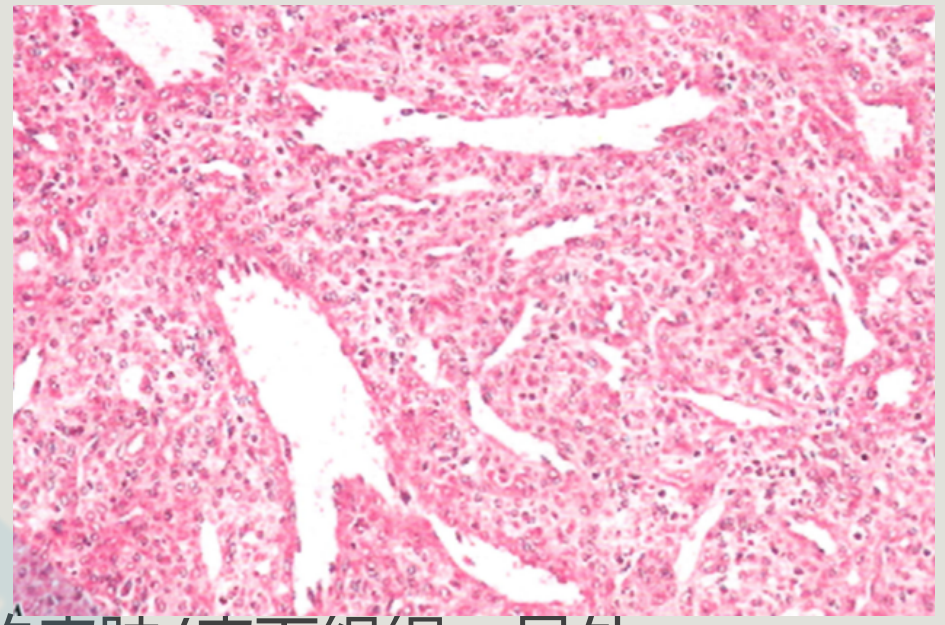
基因：CAF存在FN1-EGF基因融合

讨论5：ESFT VS CAF

相似点	鉴别点
同样存在玻璃样变区域	CAF细胞结构多样 CAF细胞束较EFST更加杂乱 CAF存在FN1-EGF基因融合 90%CAF中ERG弱阳性或中等强度表达

讨论5: Myofibroma/myofibromatosis (MF)

肌纤维瘤/肌纤维瘤病（MF）



流行病学：

从新生儿至老年人均可发病

多见于出生时和2岁以内婴幼儿

ICD-O编码：8824/0

好发部位：半数发生于头顶部、躯干、下肢和上肢的皮肤/皮下组织，另外半数发生于骨骼肌和肌腱。

组织病理学：结节状或多结节状增生，带状分布，结节周边为肥胖的肌纤维母细胞排列成短束状或旋涡状，结节中间为发育不良的圆形、多角形或梭形细胞，核稍大、深染，排列在不规则的血管外周细胞瘤样薄壁血管周围。

免疫组化：肌纤维母细胞波纹蛋白和SMA阳性

基因：经典MF存在PDGFRB基因突变，细胞型MF被报道有SRF-RELA融合。

讨论5：ESFT VS MF

相似点	鉴别点
MF经常包含肌内膜样结节增殖，这些区域可能显示一定程度的玻璃样变； 在细胞变异的MF中，梭性细胞有时可见簇状排列。	MF的梭形细胞是肥胖的 存在血管外皮瘤样血管和周细胞 ERG（-） 经典MF存在PDGFRB基因突变 细胞型MF被报道有SRF-RELA融合

讨论5：Infantile digital fibroma/fibromatosis

婴幼儿指（趾）纤维瘤病

又称包涵体纤维瘤病

流行病学：

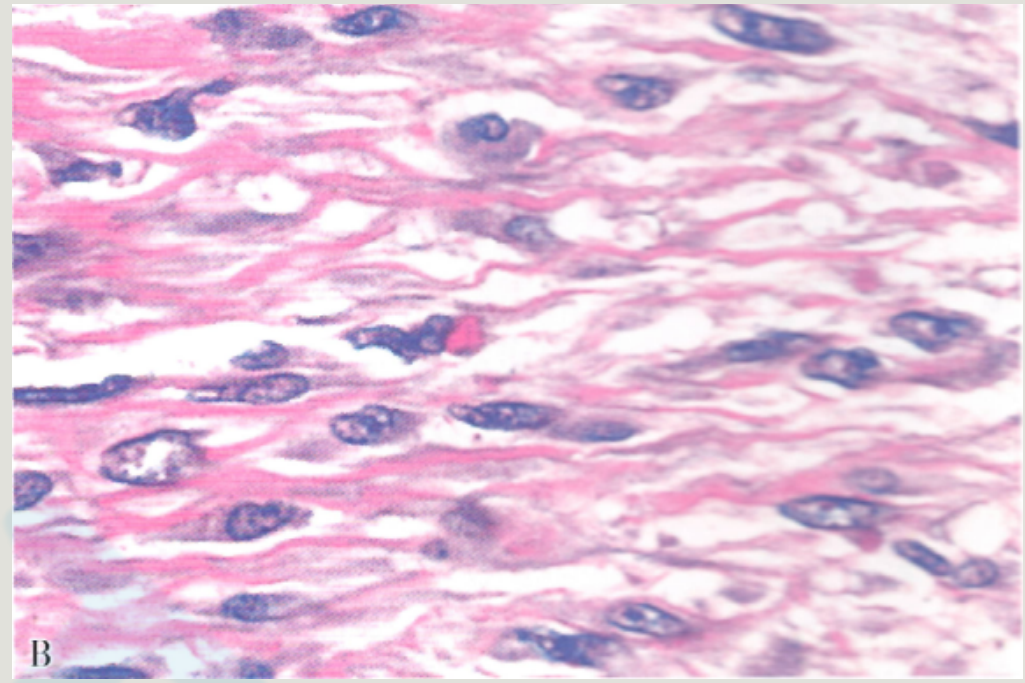
几乎仅见于婴儿、幼儿手指或足趾

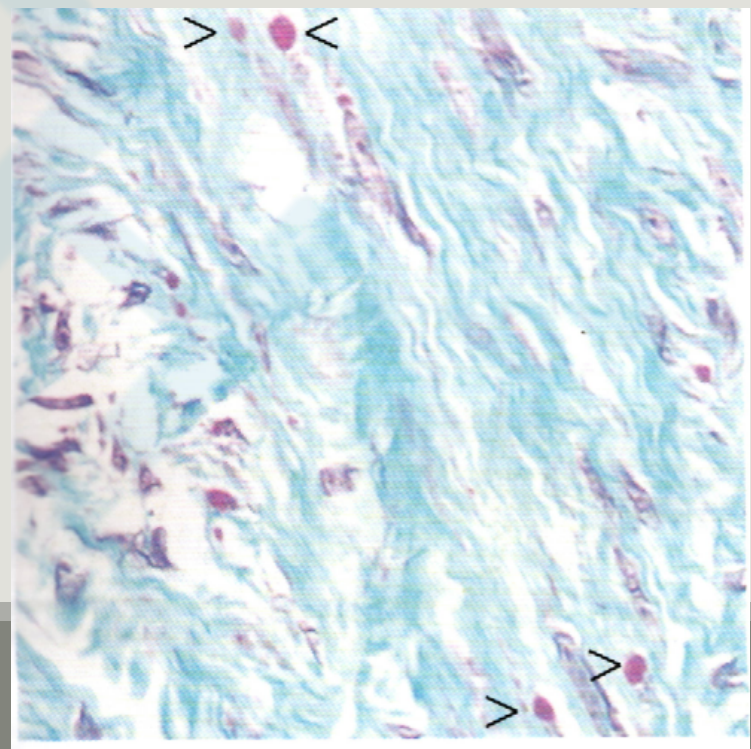
女性多于男性，多为单发

ICD-O编码：8824/0

组织病理学：真皮内有片状和束状一致性梭形细胞核数量不等的细胞外胶原，细胞质内有球形嗜酸性包涵体（Masson染色）

免疫组化：波纹蛋白和肌动蛋白阳性





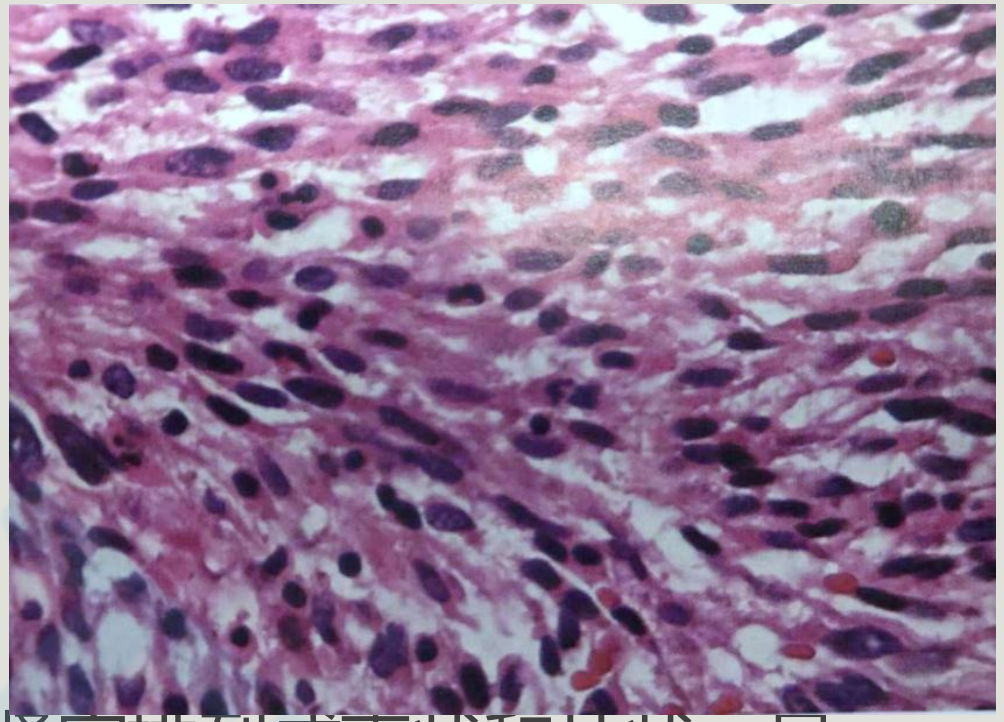
讨论5：ESFT VS Infantile digital fibroma/fibromatosis

鉴别点：

- 细胞排列成波浪样的束状或交错的短促状，与ESFT均匀的簇状排列不同
- 细胞核细长，少许嗜酸性胞浆和大量的副核内容物
- 肌肉的免疫标记（+）
- ERG（-）

讨论5：MSS

- **单相型滑膜肉瘤**



- **流行病学**：主要发生于年轻人

  男性多见，常发生于四肢深部远端

- **ICD-O编码**：9041/3

- **组织病理学**：常只含有梭形细胞成分，紧密排列成束状和片状，异型性显著。

- **免疫组化**：CK、VIM、TLE1等阳性，ERG阴性

- **基因**：SS18突变

TABLE 2. ERG Immunohistochemical Staining Characteristics of ESFT Mimics

Tumor (Acronym Used in the Text)	ERG Staining: Positive/ Tested Cases (Literature Data)
Lipofibromatosis (LPF)	0/3
Calcifying aponeurotic fibroma (CAF)	9/10 weak to moderate expression*
Lipofibromatosis-like neural tumor (LFLNT)	NA
Myofibroma/myofibromatosis (MF)	0/8 (ref. 3—0/9)
Infantile digital fibroma/ fibromatosis	0/1
Palmar/plantar fibromatosis	0/6 (ref. 3—data for desmoid-type fibromatosis—0/19)
Monophasic synovial sarcoma (MSS)	0/5 (ref. 3—0/36)

*Stained at different institution using the clone EP111; the rest stained with the clone EPR3864—for details see the Materials and methods section.

NA indicates not available.

小结

作者发现了4例伴有EWSR1-SMAD3基因融合的纤维母细胞软组织肿瘤，扩大了软组织肿瘤的病理学范畴。

这类肿瘤属于成纤维细胞/肌纤维母细胞肿瘤中高度复杂的类型中，新型而独特的一类。

作者将这类肿瘤命名为EWSR1-SMAD3基因融合的纤维母细胞肿瘤

EFG是这类肿瘤敏感的、相对特异的免疫组织化学的标记物。

THANKS