

NTRK Fusions Define a Novel Uterine Sarcoma Subtype With Features of Fibrosarcoma

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Key Words

01

NTRK

02

uterine sarcoma

03

fibrosarcoma



01

Part One

概述

子宫内膜间质及相关肿瘤

1999版	2003版	2014版
子宫内膜间质结节	子宫内膜间质结节	子宫内膜间质结节
低度恶性 ESS	低度恶性 ESS	低级别ESS
高度恶性 ESS	未分化子宫内 膜肉瘤/未分化 子宫肉瘤	高级别ESS 未分化子宫肉瘤 /未分化子宫内膜肉 瘤(不建议使用)

Kurman RJ, Carcangiu M, Herrington CS, et al. World Health Organization Classification of Tumours of Female Reproductive Organs. Lyon, France: WHO; 2014.

子宫内膜间质肉瘤 ESS

	低级别ESS	高级别ESS	未分化子宫肉瘤
生长方式	肌间脉管间浸润	肌间脉管间浸润，融合成片	内膜肌壁破坏性生长
肿瘤细胞	短梭形、卵圆形，MF <5/10HPF，灶状坏死。	异型的圆形细胞、少量梭形细胞，MF >10/10HPF，坏死多见	异型梭形细胞编织状
混合形态	平滑肌、纤维黏液样、性索样、内膜样腺体等	假乳头、假腺样，低级别ESS	横纹肌样、黏液样、低级别ESS
分子异常	CD10, ER, PR, WT1阳性；SMA, Desmin弱阳性；CD117(+)但无c-KIT突变；t(7; 17)(p21; q15)，导致JAZF1和SUZ12 (JJAZ1) 基因融合	圆细胞CD10, ER, PR(-), CyclinD1(+), 梭形细胞CD10, ER, PR(+); CD117(+)但无c-KIT突变；t(10; 17)(q22; p13)，导致YWHAE-FAM22 基因融合	CD10, ER, PR, CyclinD1不同程度表达；灶状表达SMA, Desmin, EMA, CK等。
预后	5年生存率 I - II: >90%；III - IV: 50%	常1年内复发。5年生存率介于之间	5年生存率0 (常2年内病故)

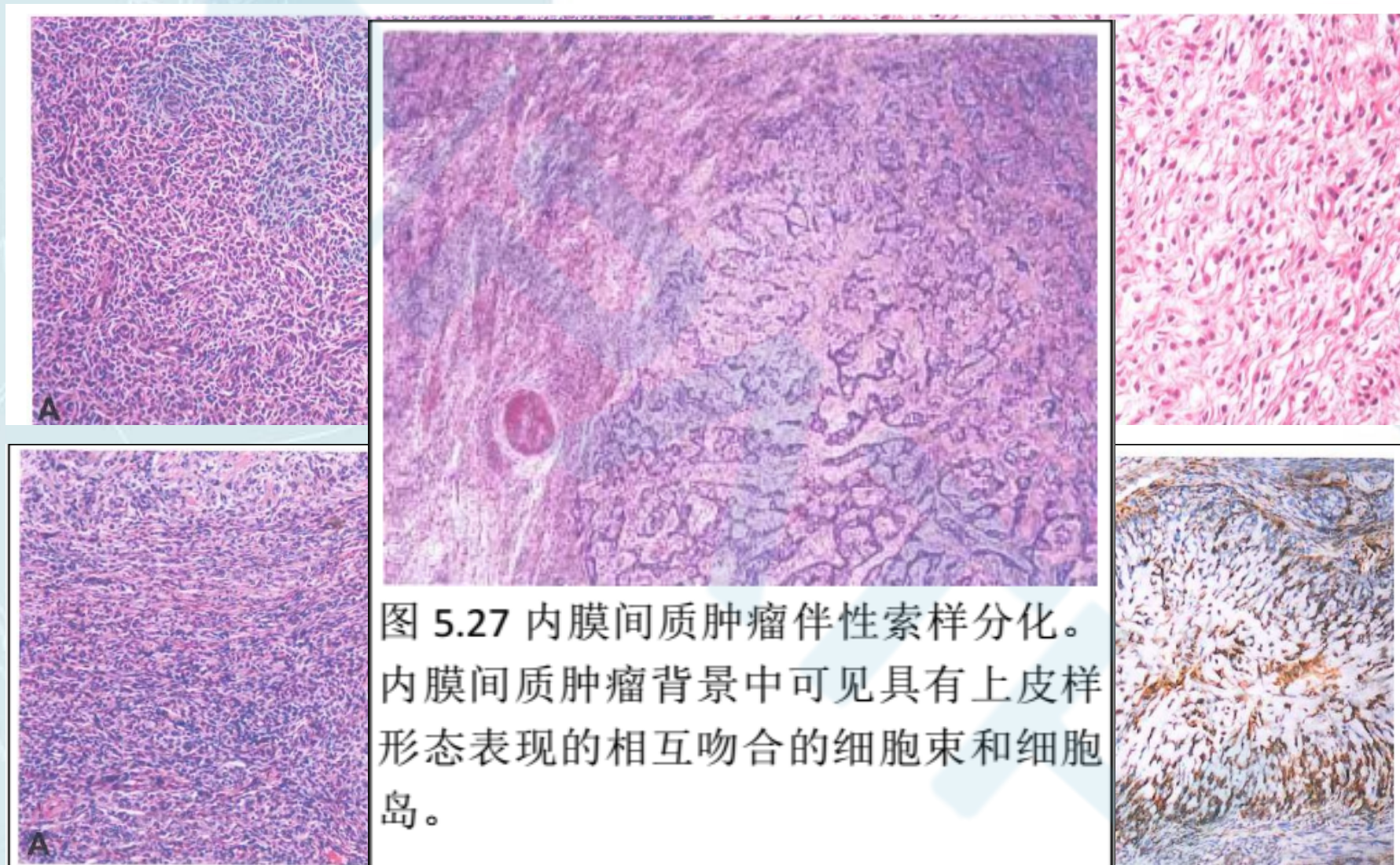


图 5.27 内膜间质肿瘤伴性索样分化。内膜间质肿瘤背景中可见具有上皮样形态表现的相互吻合的细胞束和细胞岛。

图 5.26 内膜间质肉瘤伴灶性平滑肌分化。A 内膜间质肿瘤中可见呈“星爆样”的平滑肌分化灶（底部）。B 平滑肌分化灶阳性表达 desmin。

高级别ESS

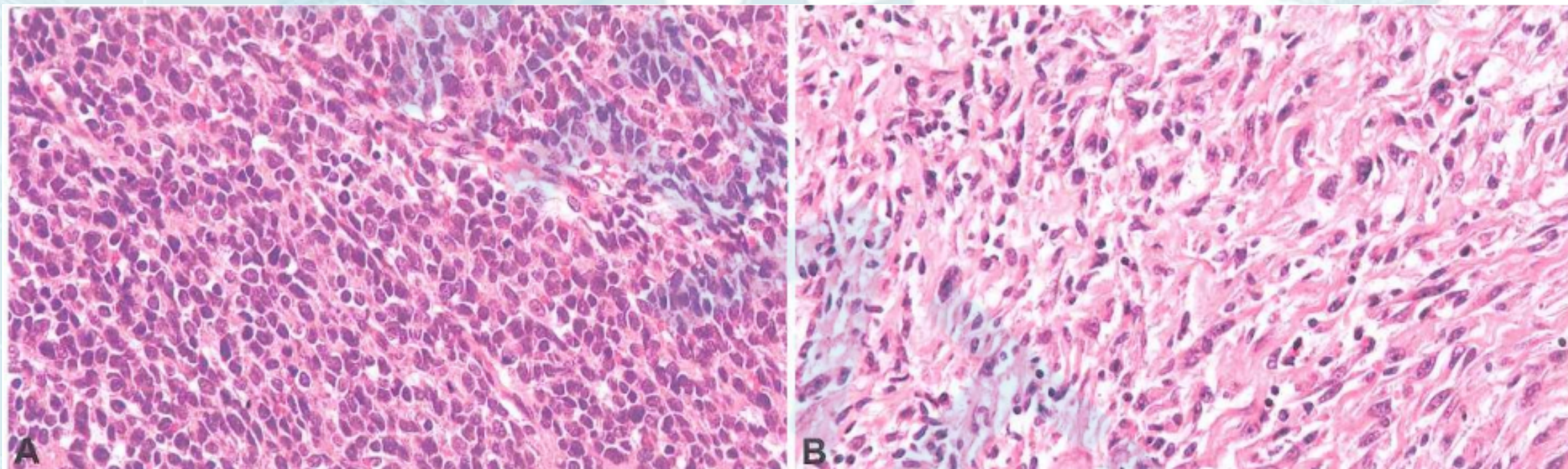
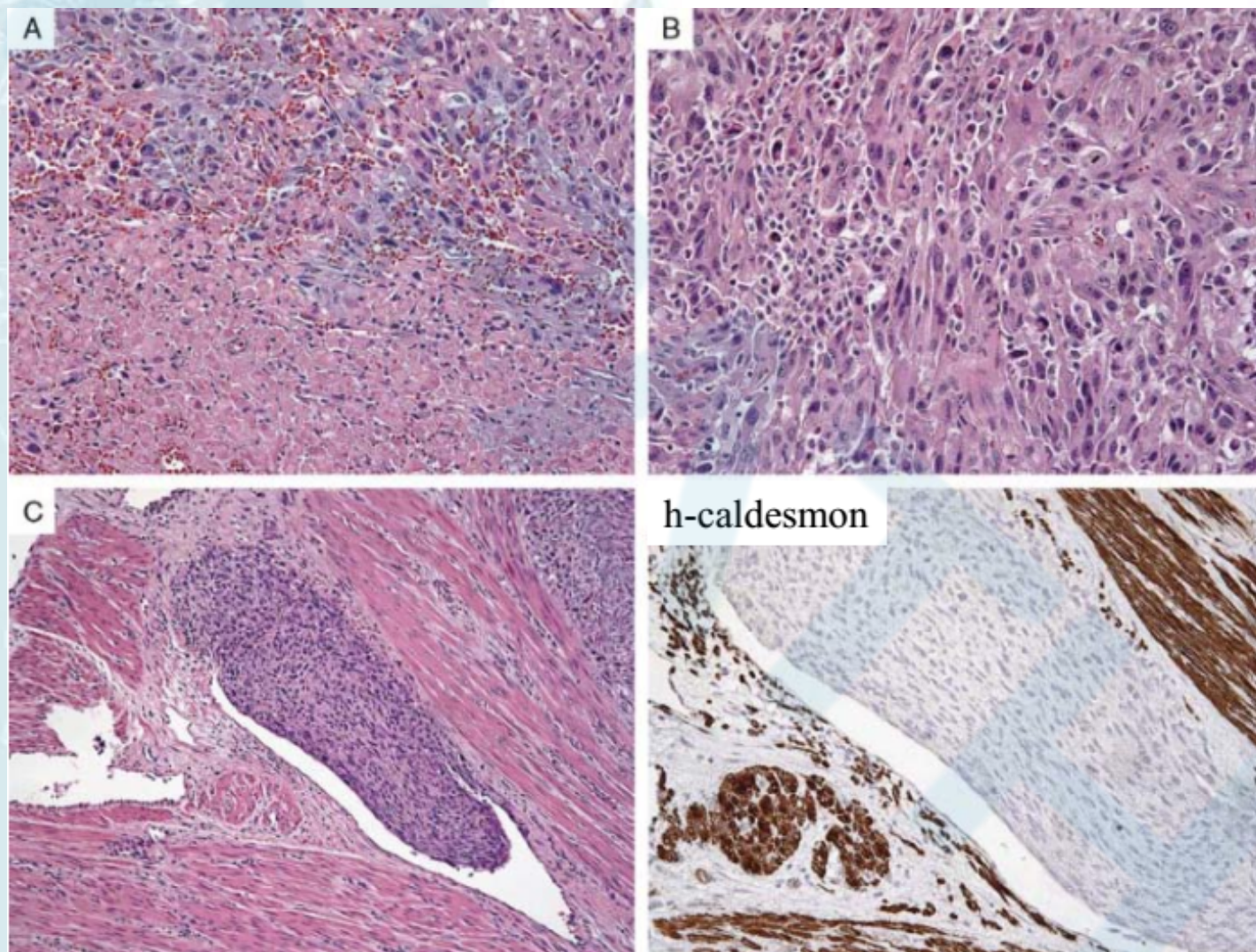


图 5.30 A 高级别子宫内膜间质肉瘤，t(10; 17)。由小圆形细胞构成，成致密巢状排列，巢间有纤细血管分隔，核分裂像多见。B 未分化子宫肉瘤。细胞高度异型，无特异性分化。瘤细胞不同于增殖期子宫内膜间质。

未分化子宫肉瘤

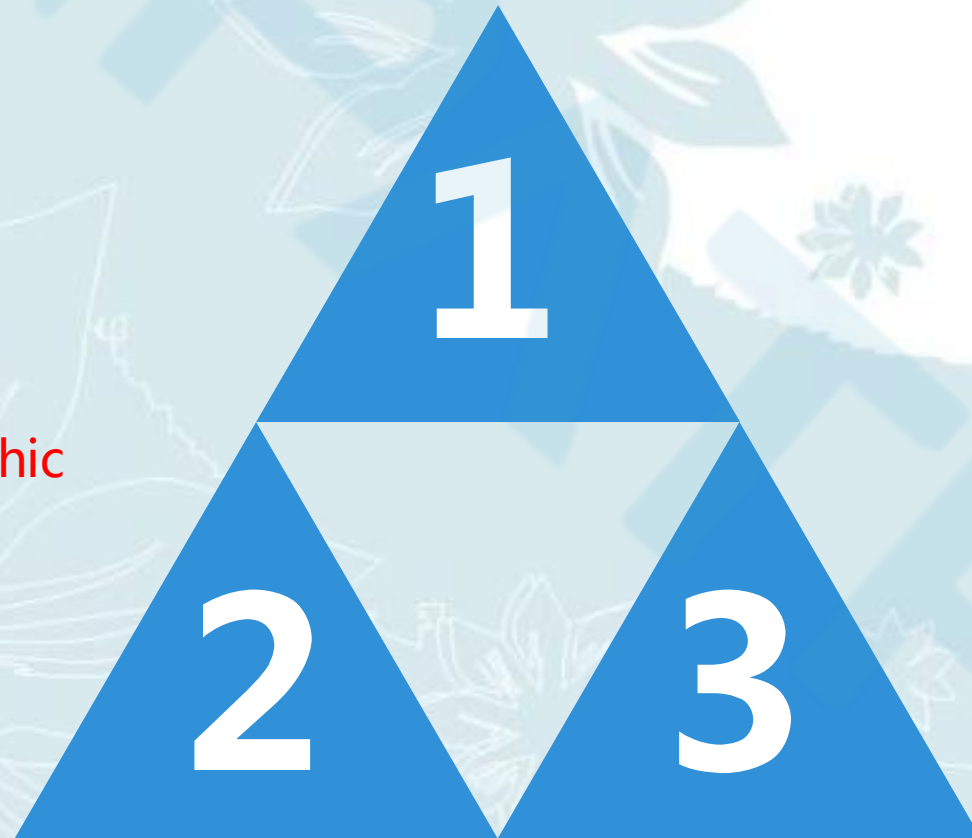


概述

未分化子宫肉瘤

similar to undifferentiated
pleomorphic sarcoma of the soft tissues.

be separable into **monomorphic**
and pleomorphic types by
morphologic assessment



harbor **TP53 mutations** in
~ 30% of cases.

*Kurihara S, et al. Endometrial stromal
sarcomas
and related high-grade sarcomas:
immunohistochemical and molecular
genetic study of 31 cases. Am J Surg Pathol.*

概述

NTRK（神经营养性酪氨酸受体激酶）基因家族：编码三种原肌球蛋白相关激酶（TrK）受体，包括NTRK1，NTRK2和NTRK3；保护中枢和外周神经系统的发育和功能。

TrK（原肌球蛋白受体激酶）：也称为高亲和力神经生长因子受体，包括TrkA，TrkB和TrkC；是人类中由NTRK基因编码的蛋白质；可导致细胞分化。发生突变与无汗，自残行为，智力迟缓和癌症有关。

An Oncogenic *NTRK* Fusion in a Patient with Soft-Tissue Sarcoma with Response to the Tropomyosin-Related Kinase Inhibitor LOXO-101

Robert C. Doebele, Lara E. Davis, Aria Vaishnavi, Anh T. Le, Adriana Estrada-Bernal, Stephen Keysar, Antonio Jimeno, Marileila Varella-Garcia, Dara L. Aisner, Yali Li, Philip J. Stephens, Deborah Morosini, Brian B. Tuch, Michele Fernandes, Nisha Nanda, and Jennifer A. Low

DOI: 10.1158/2159-8290.CD-15-0443 Published October 2015

The potential of neurotrophic tyrosine kinase (NTRK) inhibitors for treating lung cancer

Francesco Passiglia, Rafael Caparica, Elisa Giovannetti, Marco Giallombardo, Angela Listi, Patrizia Diana, ... [show all](#)

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02

Part Two

材料与方法

Case Selection

4 cases

Memorial Sloan Kettering
Cancer
Center, New York,
2014-2017, 具有梭形细胞形
态并缺乏已知遗传异常

回顾患者个人信息、临床表现、
治疗方法和预后

Methods

Immunohistochemistry (TrkA, TrkB, and TrkC)

Targeted Massively Parallel Sequencing

Whole Transcriptome RNA Sequencing

FISH (NTRK1, NTRK3, LMNA, TPR, and TPM3)



03

Part Three

结果

结果

TABLE 1. Clinical Characteristics of the Cohort

Case	Age (y)	Signs and Symptoms	Disease Site	Stage	Treatment	Outcome (mo)
1	46	Vaginal bleeding	Cervix	1B	Surgery, chemotherapy	Alive with disease, 7
2	27	Fibroid uterus	Corpus	1B	Surgery	No evidence of disease, 11
3	47	Vaginal bleeding	Cervix	1B	Surgery, chemotherapy	Died of disease, 78
4	42	Vaginal bleeding	Cervix	1B	Surgery	No evidence of disease, 2

- 中位年龄44岁（27-47）；FIGO 1B期
- 阴道异常出血，其中3例宫颈有较大肿块
- 均行全子宫+双侧附件切除术
- 患者3在首次发病后12个月出现肺转移，化疗后发生了胰腺和脑转移，最终在最初发病后78个月死亡
- 2名患者在初次就诊后11和2个月无病生存

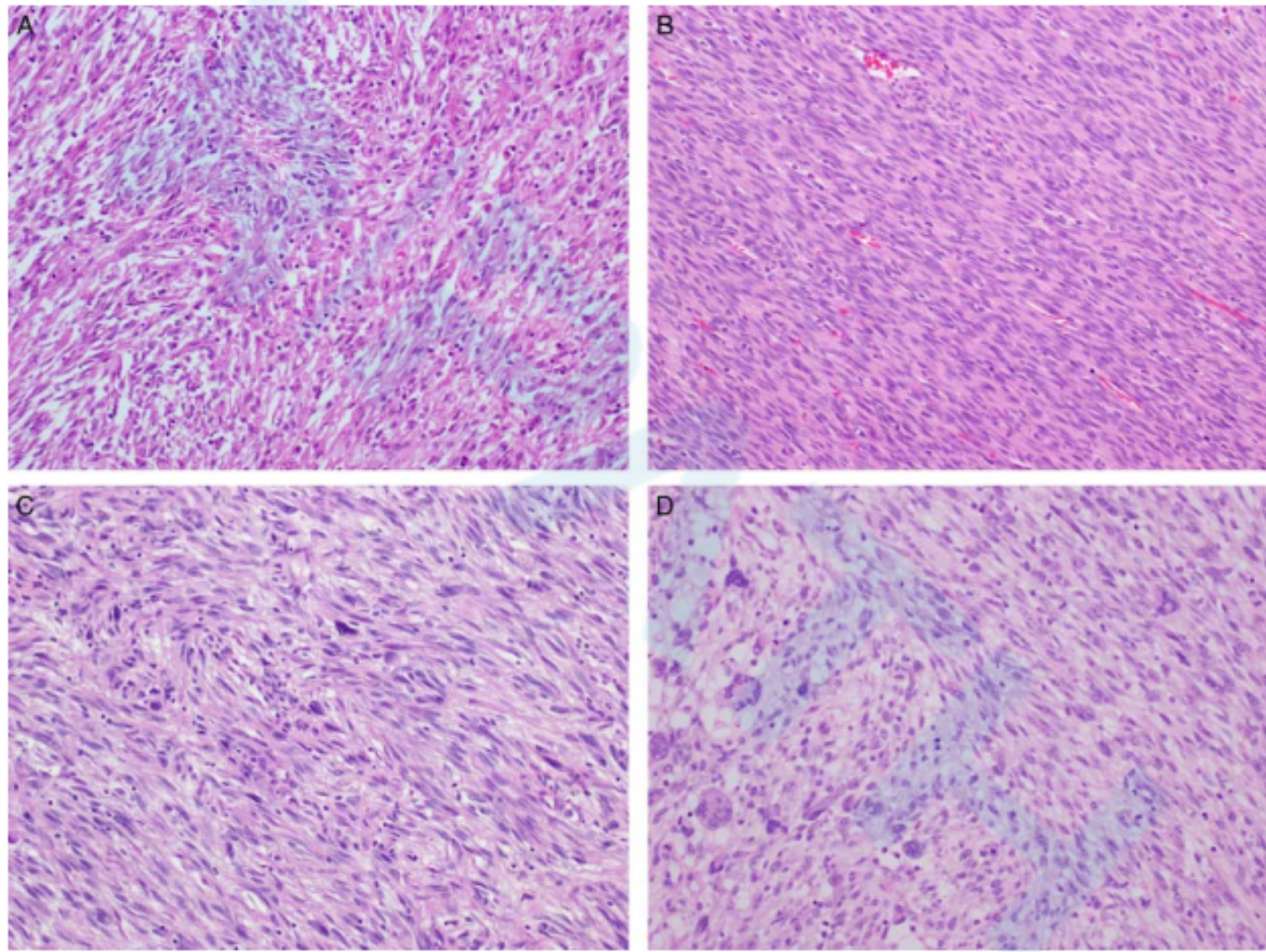
结果

TABLE 2. Gross, Morphologic, and Immunophenotypic Features of the Cohort

Case	Gross and Morphologic Features					Immunohistochemical Profile							
	Size (cm)	Atypia	Necrosis	LVI	MI	Desmin	SMA	ER	PR	CD34	S100	SOX10	H3K27me3
1	9.3	Moderate	Present	Absent	15	Neg	Pos (F)	Neg	Neg	Neg	Pos (R)	Neg	Pos
2	16.3	Moderate	Absent	Absent	7	Neg	Pos (F)	Neg	Neg	Neg	Pos (R)	Neg	Pos
3	14.0	Moderate	Present	Absent	12	Neg	Pos (F)	Neg	Neg	Neg	Pos (R)	Neg	Pos
4	2.6	Severe	Absent	Absent	30	Neg	Pos (F)	Neg	Neg	Neg	Pos (R)	Neg	Pos

F indicates focal; LVI, lymphovascular invasion; MI, mitotic index (number of mitotic figures/10 high power fields); Neg, negative; Pos, positive; R, rare cells.

结果



结果

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2	16.3	Moderate	Absent	Absent	7	Neg	Pos (F)	Neg	Neg	Neg	Pos (R)	Neg	Pos
3	14.0	Moderate	Present	Absent	12	Neg	Pos (F)	Neg	Neg	Neg	Pos (R)	Neg	Pos
4	2.6	Severe	Absent	Absent	30	Neg	Pos (F)	Neg	Neg	Neg	Pos (R)	Neg	Pos

F indicates focal; LVI, lymphovascular invasion; MI, mitotic index (number of mitotic figures/10 high power fields); Neg, negative; Pos, positive; R, rare cells.

阳性：SMA, S100, H3K27me3

阴性：Desmin, ER, PR, CD34, SOX10

结果

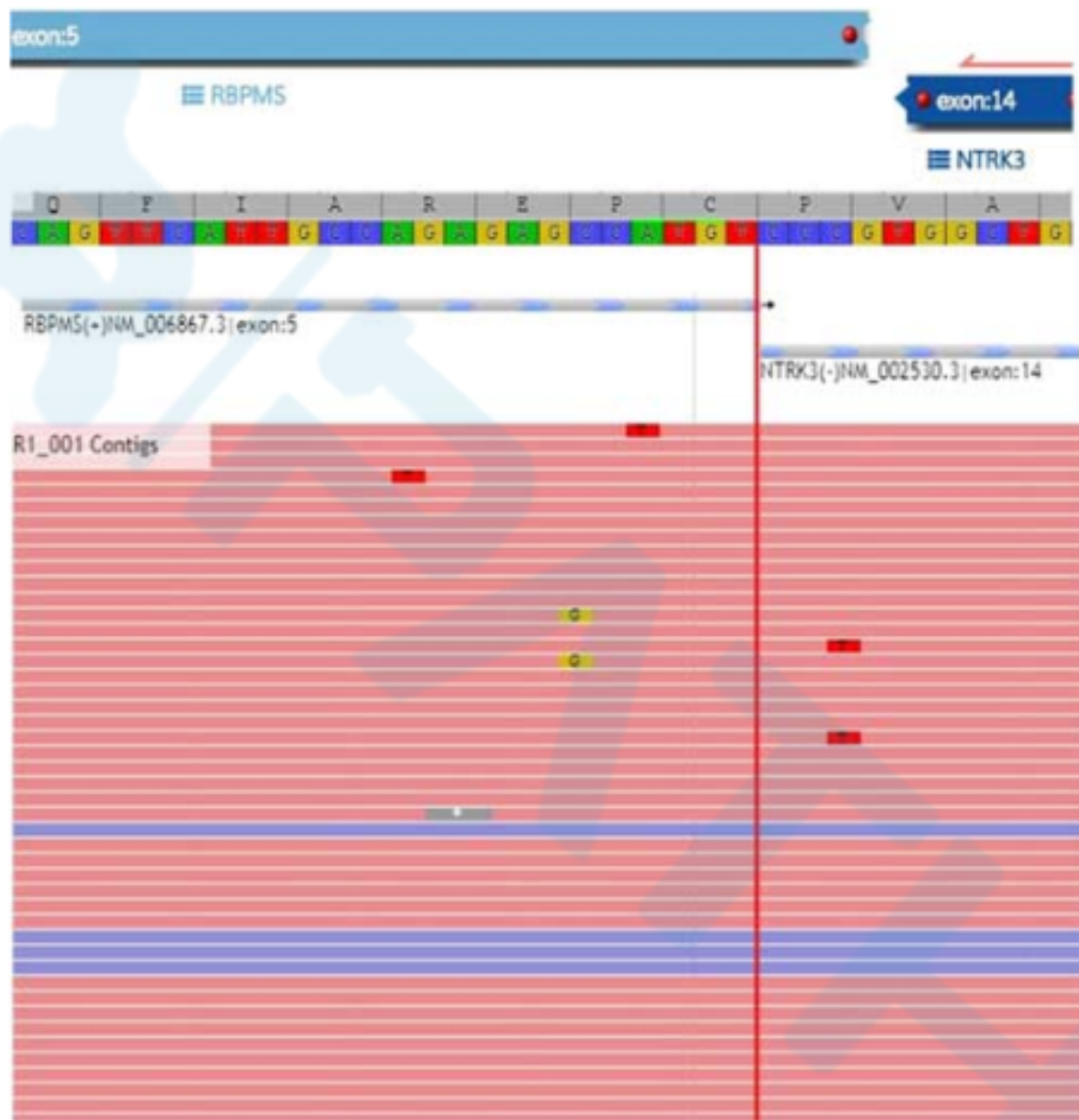


FIGURE 2. Confirmation of *RBPMS-NTRK3* fusion in a uterine sarcoma by targeted RNA sequencing.

结果

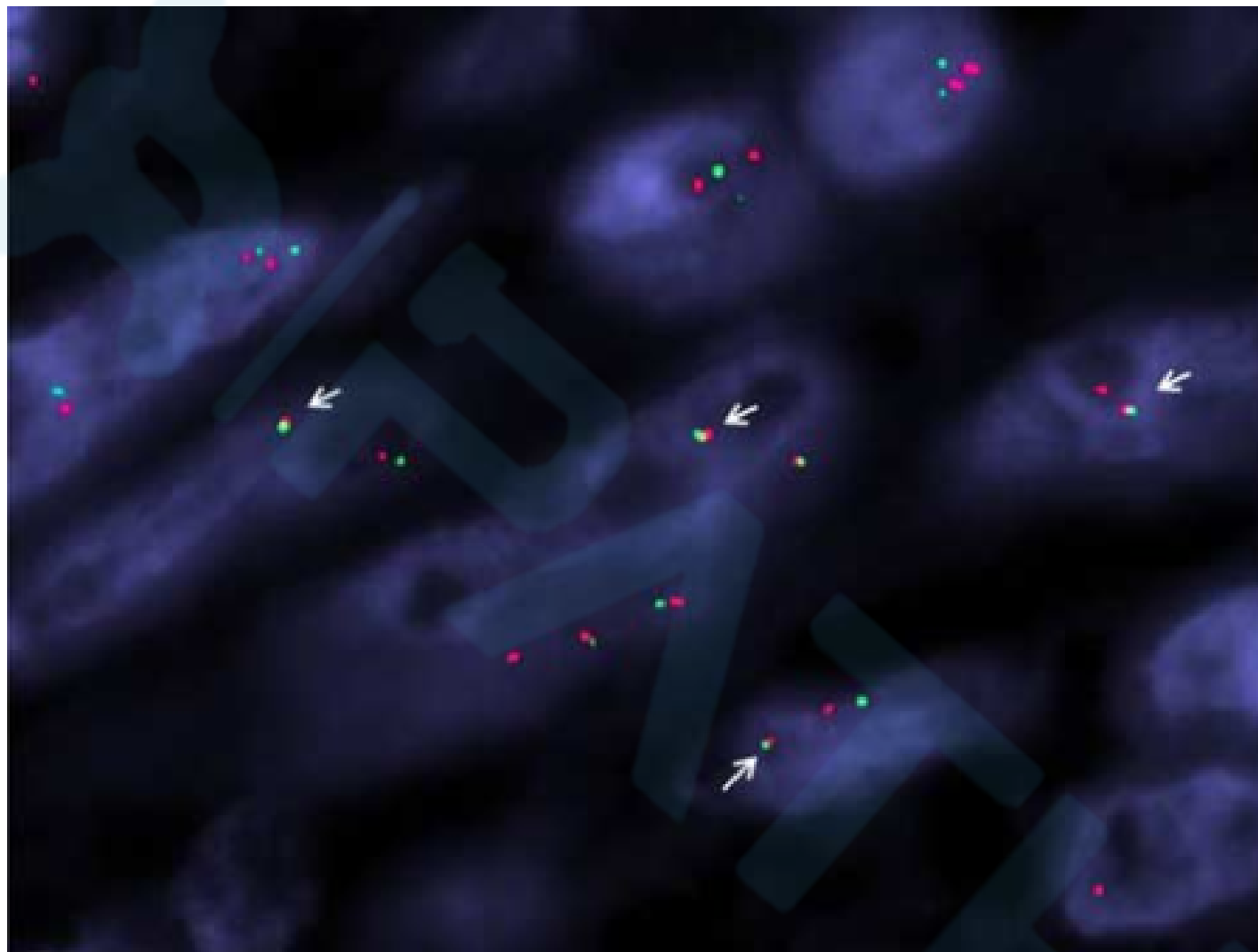
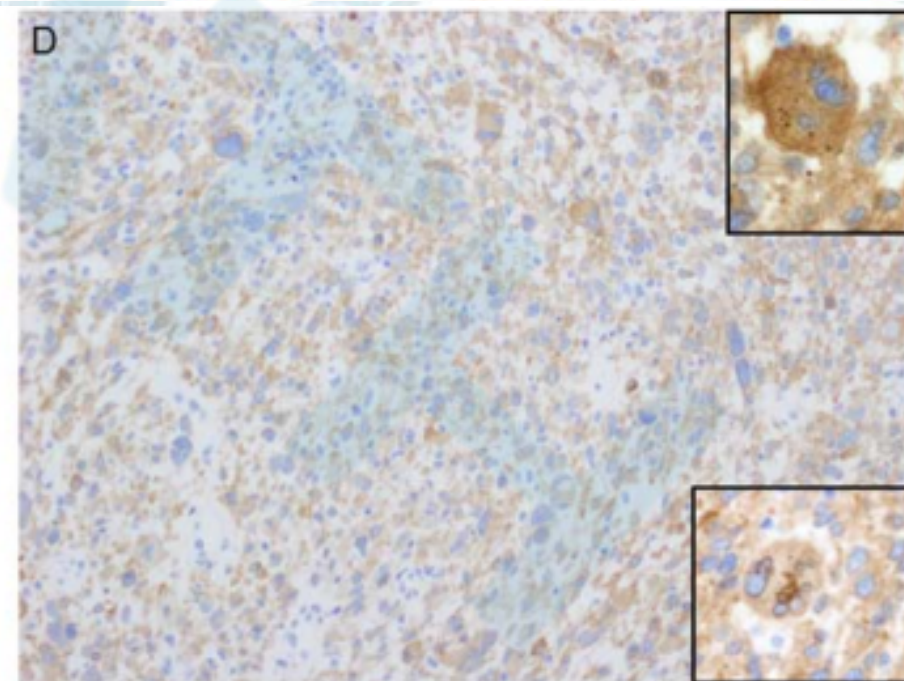
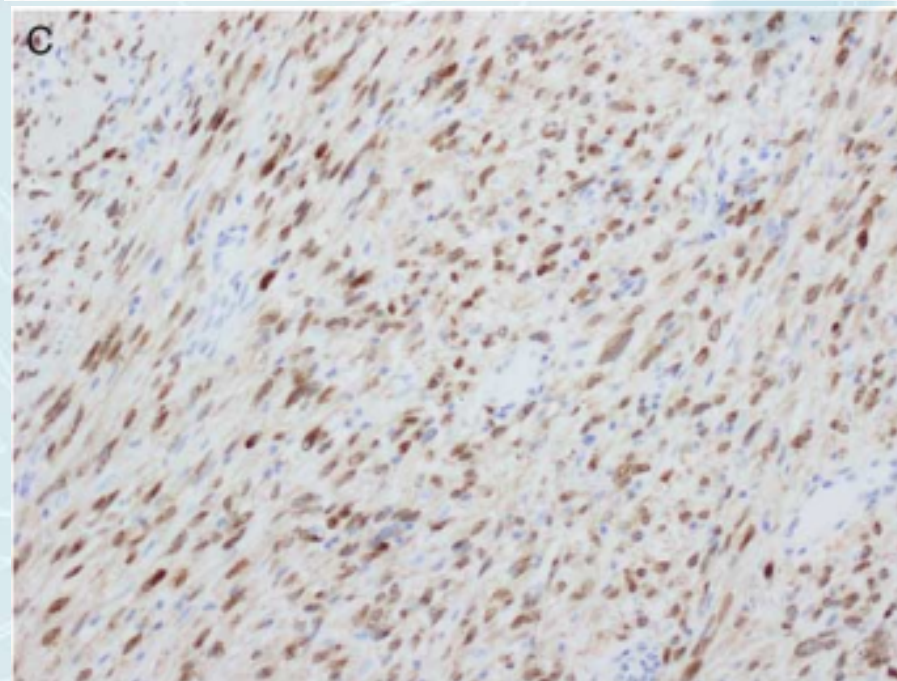
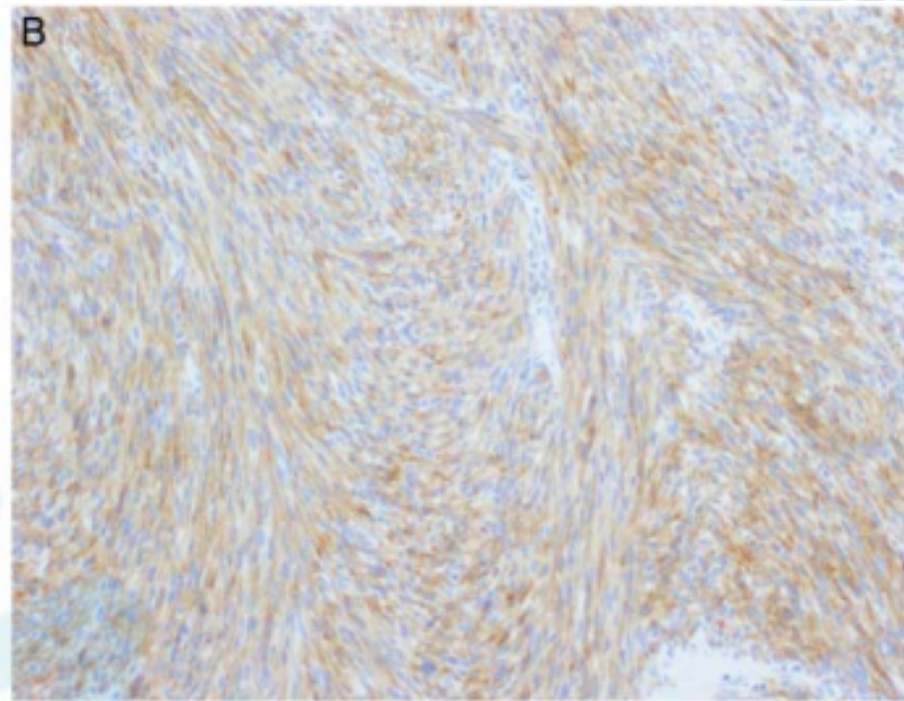
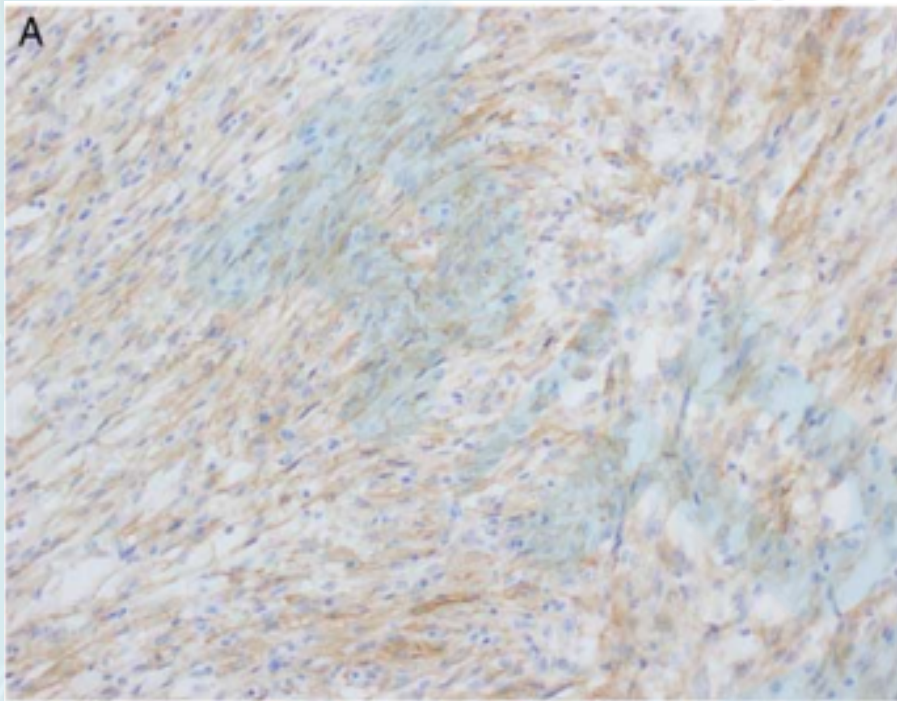


FIGURE 3. *LMNA-NTRK1* gene fusion demonstrated by FISH. A 2 color-fusion assay was applied showing the *NTRK1* (green, telomeric) and *LMNA* (red, centromeric) signals come together as a yellow fused signal (white arrows).

结果





04

Part Four

讨论

讨论

01

首次报道了NTRK基因融合的一组未分化的子宫肉瘤中存在纤维肉瘤样形态

02

通过免疫组织化学检测所有肿瘤均表达TrkA或pan-Trk

03

NTRK基因融合在大多数常见癌症中很少见，例如肺癌和结直肠癌

04

ETV6-NTRK3融合和NTRK1基因重排分别定义了大多数婴儿纤维肉瘤和脂肪纤维瘤样神经肿瘤

梭形细胞平滑肌肉瘤

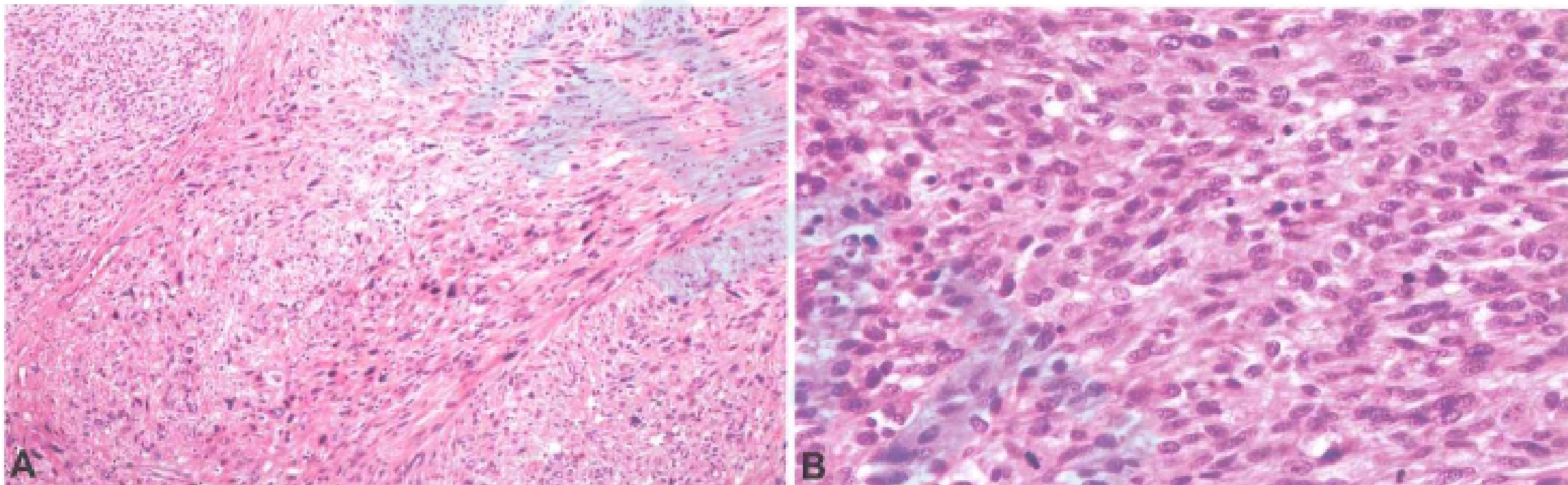


图 5.22 梭形细胞平滑肌肉瘤。A 肿瘤由交错束状排列的高度异型的梭形细胞构成。B 梭形细胞核有异型性，核分裂像容易见到。

总结



01

揭示了新的高级别子宫肉瘤亚型，具有软组织纤维肉瘤的特征，通过复发的NTRK基因融合对Trk进行致癌活化，证明这些病变是一种独特的临床病理实体。

02

建议将这些肿瘤分类为NTRK融合阳性子宫梭形细胞肉瘤，不同于平滑肌肉瘤。

03

在这类肿瘤中评估Trk表达和NTRK融合状态可以使患者从选择性抑制Trk信号传导的临床试验中受益。

THANK YOU

