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ORIGINAL ARTICLE

SMARCA4-deficient Uterine Sarcoma and Undifferentiated Endometrial Carcinoma Are Distinct Clinicopathologic Entities

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背景

未分化和去分化子宫内膜癌UDEC

定义

子宫内膜未分化癌是一种没有分化方向的上皮性恶性肿瘤。去分化癌由未分化癌和 FIGO 1 级或 2 级子宫内膜样癌混合构成。

ICD-O 编码

未分化癌 8020/3

流行病学

未分化癌罕见，可能与 Lynch 综合征相关。

临床特征

一项研究显示，未分化癌患者中位年龄为 55 岁。多数患者表

大体检查

多数未分化癌形成大的息肉状腔内肿块，大小 2cm~15cm。累及子宫下段。

组织病理学

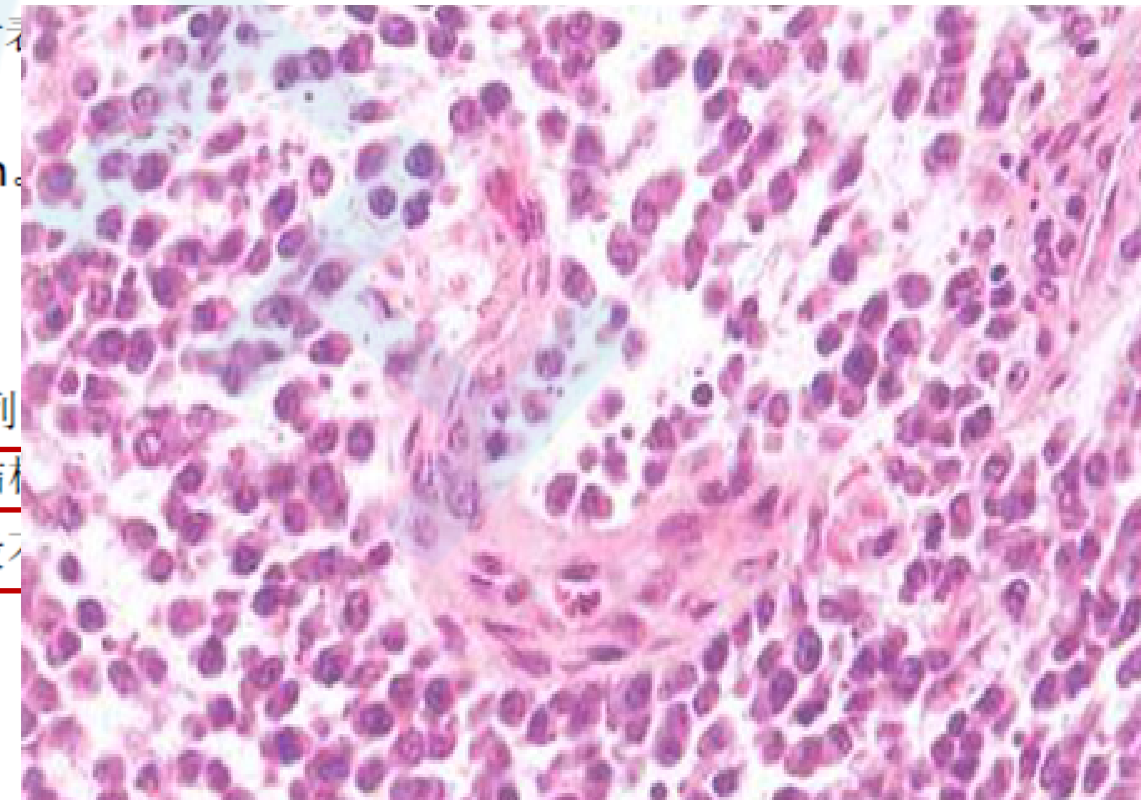
单形性未分化癌

细胞缺乏黏附性，大小相对一致，小至中等大小，成片排列

浆细胞瘤、“高级别子宫内膜间质肉瘤”或小细胞癌。无腺样结构

个/10HPF。在单形性背景中偶可见到多形性核。间质成分一般不

有大量淋巴细胞浸润。



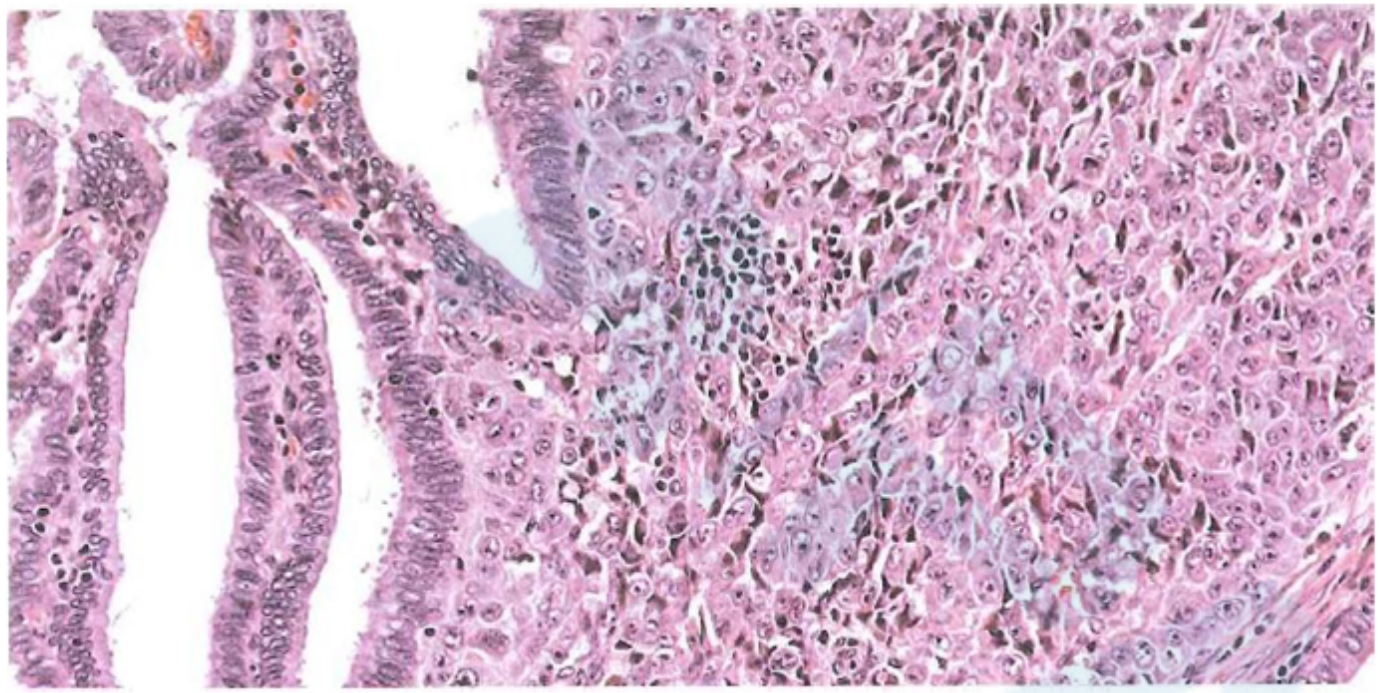


图 5.09 未分化癌，也可称为去分化癌。左侧的高分化癌邻接右侧的未分化癌。

去分化癌

约 40%的单形性未分化癌中还可见到第 2 种成分，后者表现为 FIGO 1 级或 2 级子宫内膜样癌，这种现象被描述为“去分化癌”。分化型子宫内膜样成分一般衬覆于子宫腔面，而未分化成分在其下方生长。

免疫组织化学

未分化癌中，仅散在细胞有上皮分化证据，这些细胞强阳性表达 EMA 和 CK18，不表达 pan-CK。瘤细胞表达 vimentin，但不表达 ER、PR、E-cadherin。少数细胞可表达嗜铬粒蛋白和/或 Syn。

组织起源

一些肿瘤可能通过去分化过程发展而来。

遗传学特征

约半数病例有高度微卫星不稳定性，伴 *MLH1* 启动子甲基化，以及 MLH1 和 PMS2 表达缺失。

遗传易感性

已有报道罕见的未分化癌发生于 Lynch 综合征患者。

预后和预测因素

肿瘤具有高度侵袭性，55%~95%的病例出现复发或致死。

04. 未分化子宫肉瘤

定义

起源于子宫内膜和肌壁、与增殖期子宫内膜间质完全不同、具有高级别细胞学特征，且缺乏特异性分化的肿瘤。

ICD-O 编码 8805/3

同义词

未分化子宫内膜肉瘤（不推荐）

流行病学

未分化子宫肉瘤罕见。一般见于绝经后，平均年龄 60 岁。

临床特征

约 2/3 患者分期高（Ⅲ/Ⅳ期）。一般表现为绝经后出血，或继发于子宫外扩散的症状/体征。

大体检查

多为腔内息肉状肿块，直径一般>10cm，切面呈鱼肉样，可见坏死和/或出血区。

组织病理学

低倍镜下，肿瘤境界不清，破坏性浸润肌壁。瘤细胞成片状排列，可见席纹状或鲱鱼骨样结构，细胞异型性显著。有可能出现横纹肌样形态或黏液样背景。核分裂像多见，包括病理性核分裂，常见淋巴管浸润。罕见肿瘤可与 LGESS 突然过渡，提示部分肿瘤起源于子宫内膜间质（“去分化低级别子宫内膜间质肉瘤”）

免疫组织化学

肿瘤不同程度表达 CD10，阴性或弱阳性表达 ER、PR。可弥漫阳性表达 cyclin D1，但这样的肿瘤同时阳性表达 CD10（这不同于 *YWHEA-FAM22* 肉瘤）。可局灶性表达 SMA、desmin、EMA 或 CK。

组织起源

未分化子宫肉瘤的起源未明，但微小 RNA 研究显示，少数肿瘤可能起源于子宫内膜间质。

遗传学特征

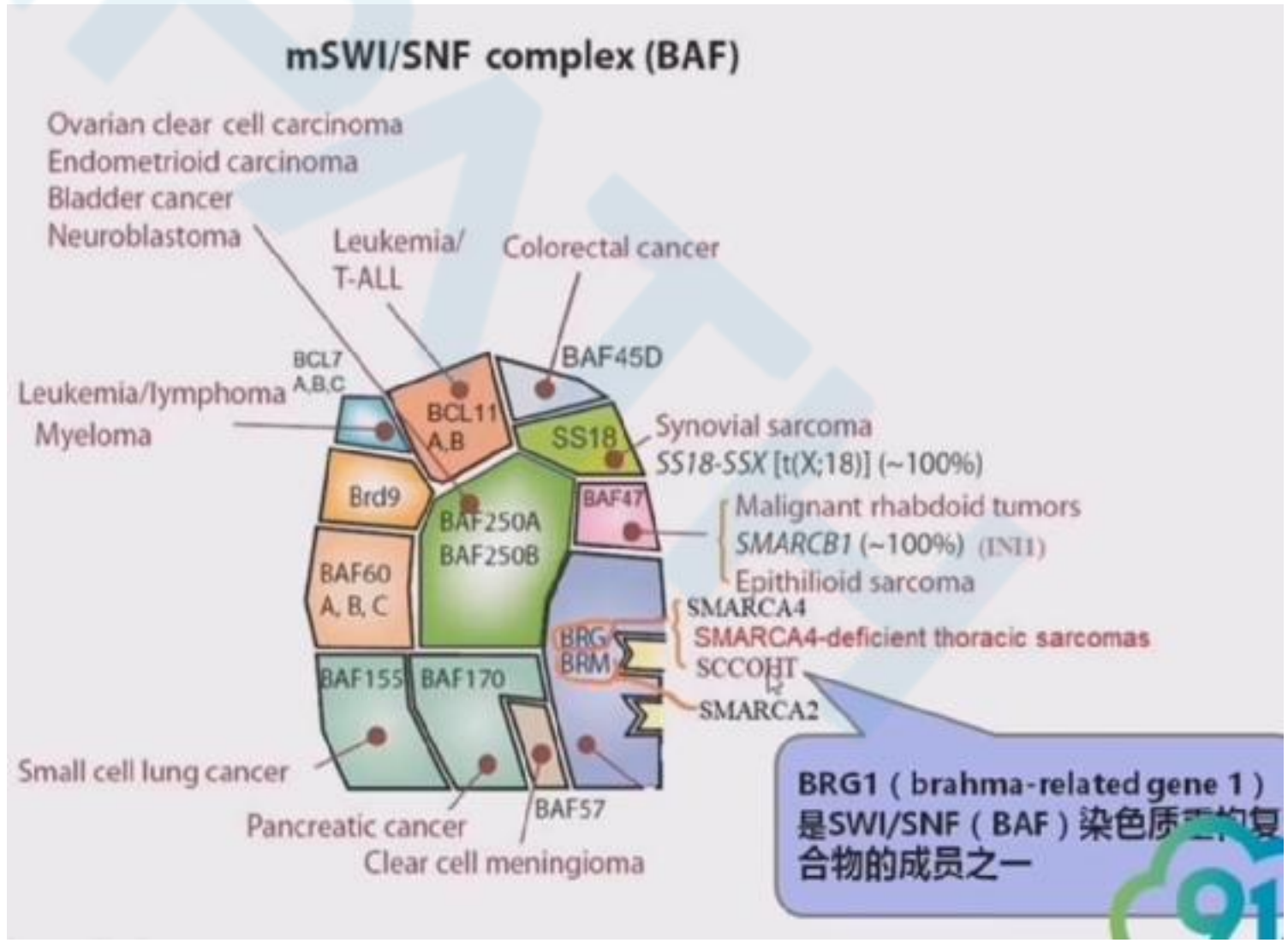
未分化肉瘤有复杂的染色体改变，包括 2q、4q、6q、7p、9q 和 20q 获得，以及 3q、10p 和 14q 缺失。

预后和预测因素

多数患者（>60%）处于晚期。即使Ⅰ期肿瘤患者也一般于 2 年内死亡。辅助治疗对预后无明显改善。

SWI/SNF复合物

- SWI/SNF复合物是ATP依赖性染色体重塑复合物家族成员，可利用ATP水解能促使染色体构象改变，使转录因子易于接近核小体DNA，从而对基因转录进行调控。
- 其核心成员包括BRM(SMARCA2)、**BRG1(SMARCA4)**、INI1(SMARCB1、SNF5或BAF47)、ARID1A(BAF250A) 和PBRM1(BAF180)。其核心亚基的失活与多种肿瘤关系密切。



MENU

MODERN PATHOLOGY

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SMARCA4-deficient undifferentiated uterine sarcoma (malignant rhabdoid tumor of the uterus): a clinicopathologic entity distinct from undifferentiated carcinoma

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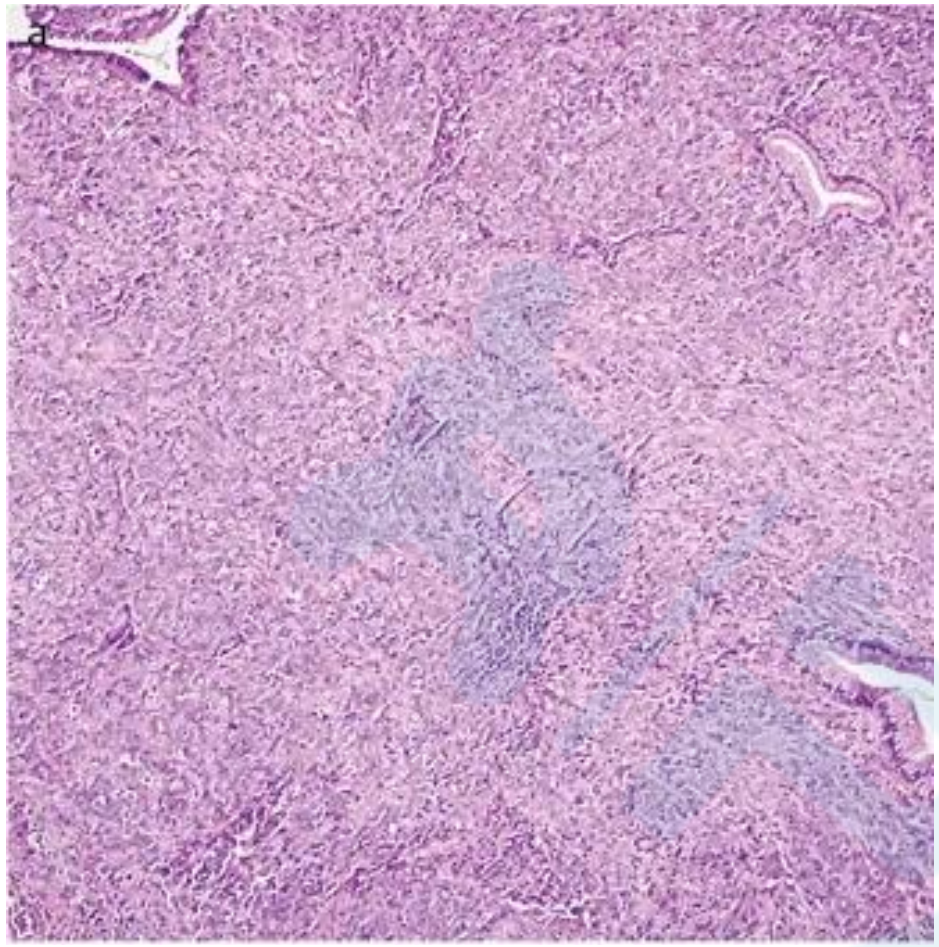
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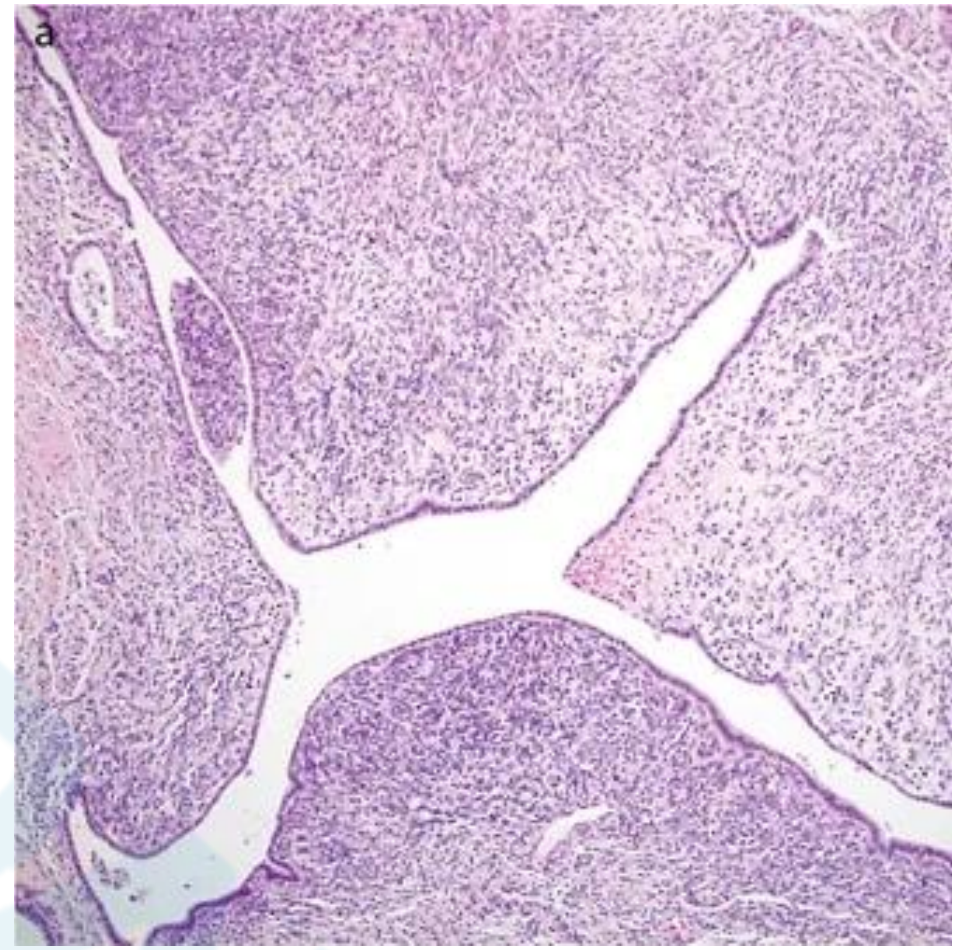
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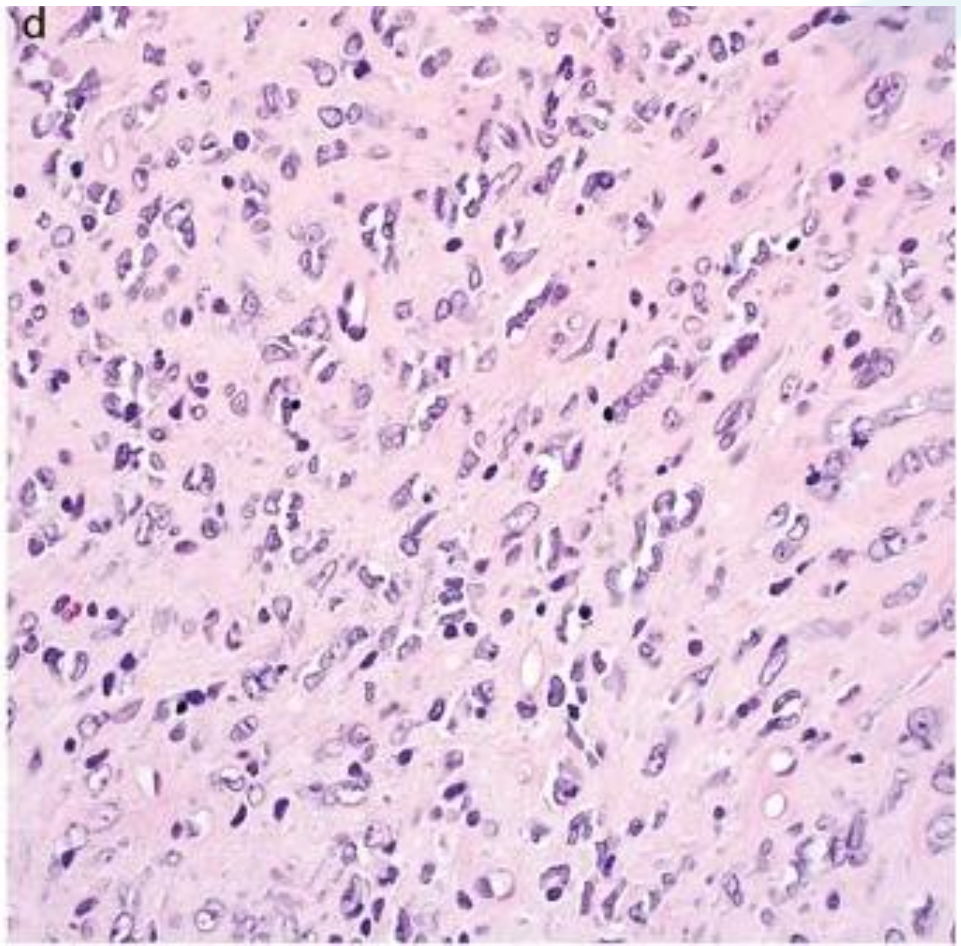
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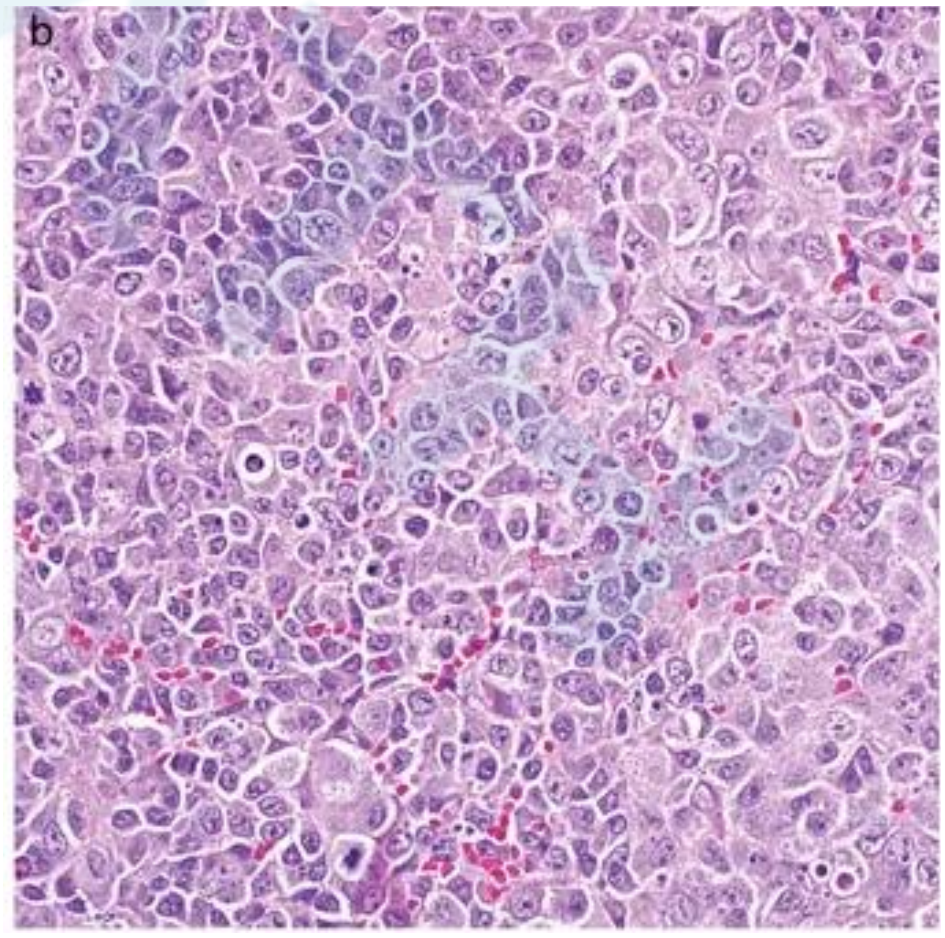
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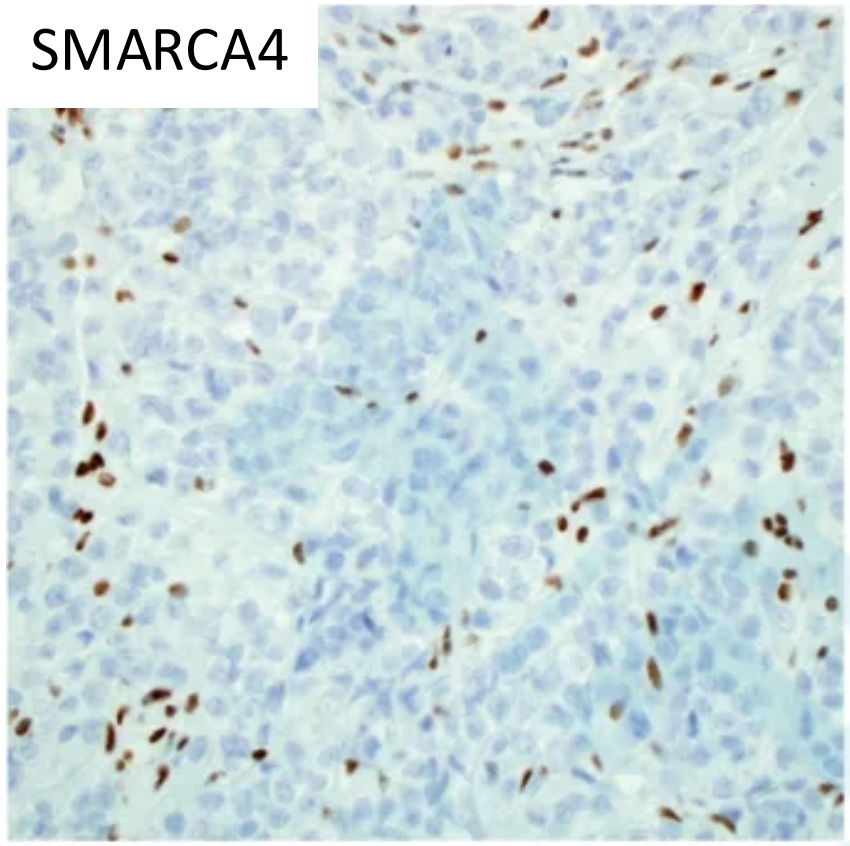
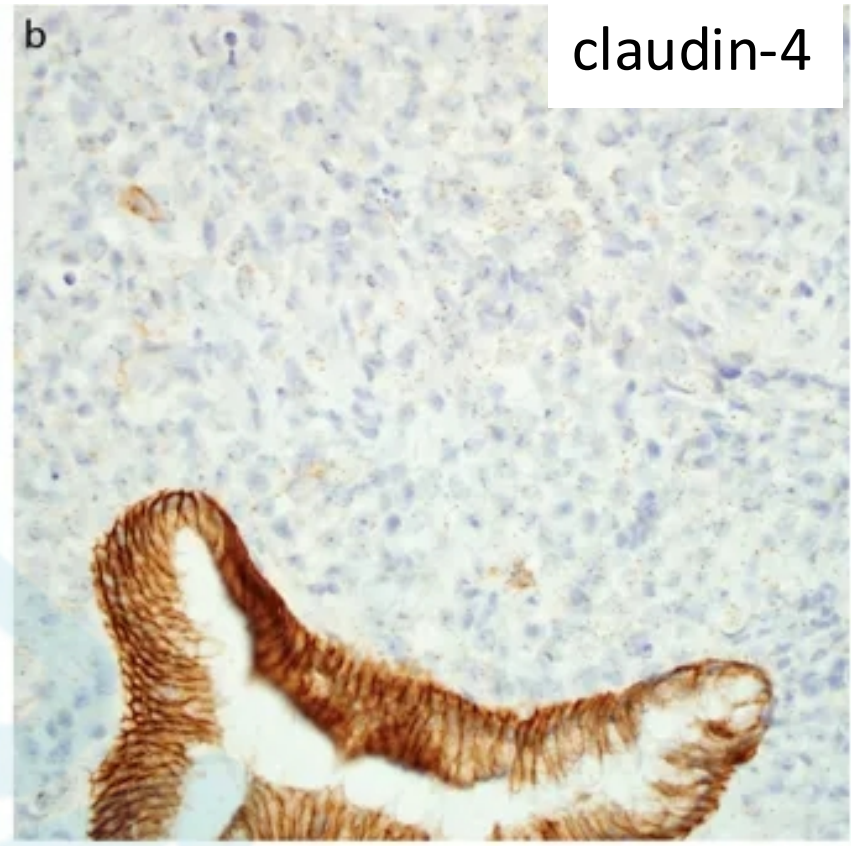
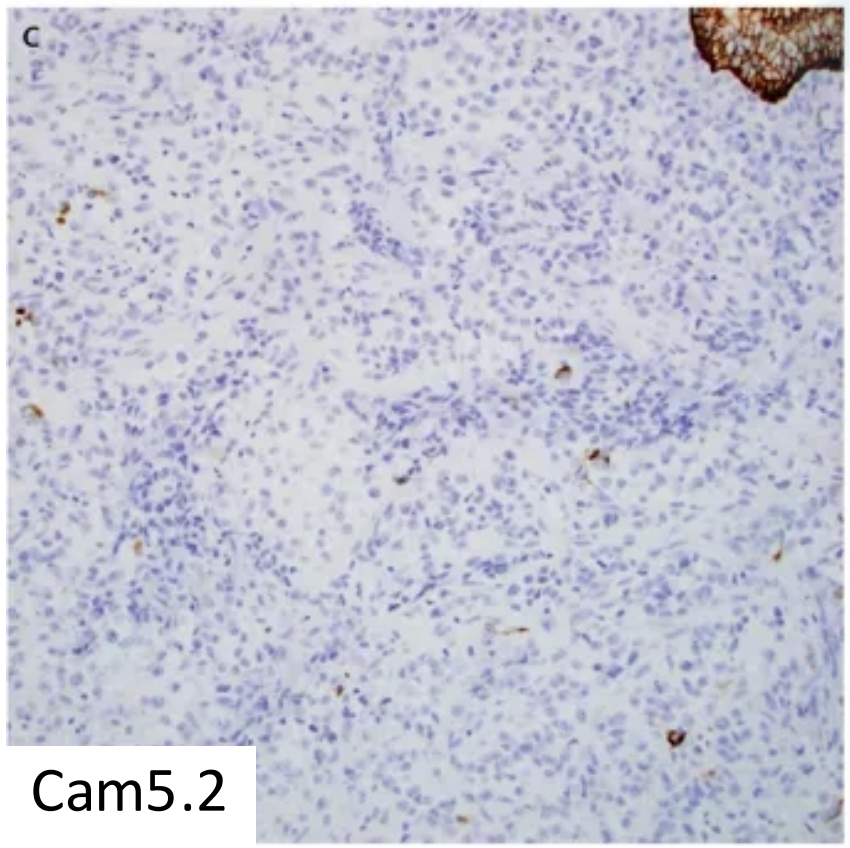
SMARCA4

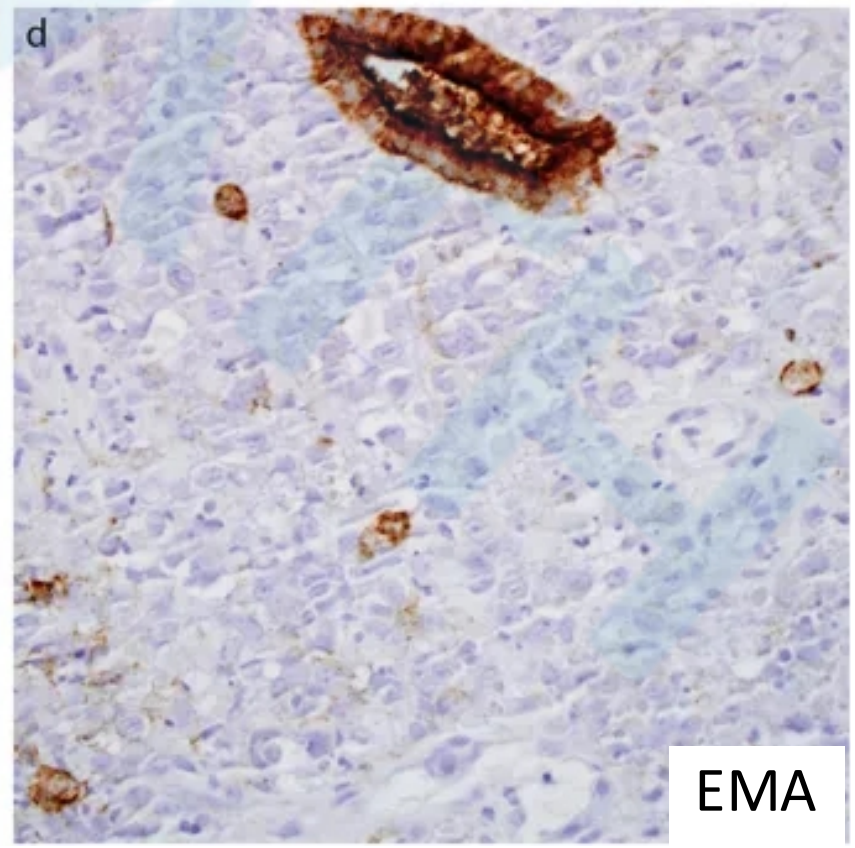




claudin-4



Cam5.2



EMA

Table 2 Clinicopathologic features of cases of SMARCA4-deficient undifferentiated uterine sarcoma/malignant rhabdoid tumor of the uterus

From: SMARCA4-deficient undifferentiated uterine sarcoma (malignant rhabdoid tumor of the uterus): a clinicopathologic entity distinct from undifferentiated carcinoma

Case	Age (years)	Follow-up	MMR IHC	SMARCA4 IHC	Claudin-4 IHC	SMARCB1 IHC	WT-1 IHC	HMB-45 IHC	Genomic alterations
1	25	DOD at 7 months	Intact	Lost	Negative	Intact	Negative	Negative	Failed MPS
2	33	DOD at 9 months	Intact	Lost	Negative	Intact	Negative	Negative	*SMARCA4* c.3426delC frameshift *SMARCA4* c.4759G>T nonsense *TERT* promoter mutation
3	34	DOD at 1 month	Intact	Lost	Rare cells	Intact	Positive	ND	*SMARCA4* c.2554A>T nonsense *ASXL1* c.1205G>A, p.R402Q missense
4	29	DOD at 4 months	ND	Lost	Negative	ND	ND	Negative	*SMARCA4-PSG8* inversion *ARID1B* c.5687G>A, p.R1896Q missense
5	58	DOD at 43 months	ND	ND	ND	Intact	ND	Negative	*SMARCA4* c.582_587GCCCCT>G frameshift *NPRL2* c.428G>A *SH2B3* c.1666G>A *SMARCA4* c.598C>G, p.L200V (VUS) *ZNF217* c.2061_2061A>TTA frameshift

MMR mismatch repair, DOD dead of disease, VUS variant of uncertain significance, ND not done

SMARCA4-缺陷型未分化子宫肉瘤SDUS

- 虽然与未分化癌有明显的形态重叠，但有独特的临床病理特征，包括年轻；形态学表现为具有横纹肌样形态的弥漫性细胞片，大的上皮样细胞、泡状核、核仁显著；免疫组化SMARCA4表达缺失、SMARCB1和MMR染色完整，角蛋白、EMA、claudin-4等上皮标志物阴性；临床表现为高侵袭性、高浸润性、广泛的淋巴血管浸润和子宫外播散；分子改变以SMARCA4的功能缺失为特征，几乎没有其他基因组异常，更类似卵巢小细胞癌、高钙血症型(SCCOHT)。

目的

- 收集更多的病例，从临床特征、形态学、免疫组化和分子生物学对SMARCA4-缺陷型未分化子宫肉瘤及其与未分化和去分化子宫内膜癌的区别做出更详尽的研究

材料和方法

病例筛选

- 未分化和去分化子宫内膜癌UDEC：共84例（包括未分化(n=12)和去分化(n=17)子宫内膜癌及来自文献55例）
- SMARCA4-缺陷型未分化子宫肉瘤SDUS：12例（含之前报道的5例）
- 对所有病例形态结构进行回顾：淋巴管侵犯、核多形性（定义为在×4倍镜下可见的异型性）、坏死、间质透明变、核分裂活性、不典型核分裂和叶状结构（定义为肿瘤细胞围绕良性上皮细胞形成的叶状结构）

免疫组化及大规模平行测序MPS

BRG1(SMARCA4	clone ERP3912, 1:50 dilution,Abcam,Cambridge, MA
BAF47 (aka INI-1)	clone 25, 1:250 dilution, BD Biosciences, Woburn, MA
P53	clone DO-7, 1:500 dilution, Dako, Carpinteria, CA
Claudin-4	clone 3E2C1, 1:500 dilution, Invitrogen, Carlsbad, CA
SMARCA2	polyclonal, 1:400 dilution, Atlas Antibodies,Bromma, Sweden
MSH2	clone FE11, 1:200 dilution,Oncogene Research Products, La Jolla, CA
MSH6	clone PU29, 1:50 dilution, Leica Biosystems, Buffalo Grove, IL
MLH1	clone NCL-L-MLH1, 1:100 dilution,Leica Biosystems
PMS2	clone MRQ-28, 1:50 dilution,Cell Marque, Rocklin, CA

- >5%的肿瘤细胞细胞膜阳性，则认为Claudin-4阳性。
- 对于去分化癌，免疫组化在未分化成分中评估。

结果

临床病理特征

- SDUS发病年龄**明显低于**UDEC（平均35.8y；中位值33.5y；范围24-58y vs. 平均61.2y；中位数61y；范围23-93y; P=0.0001）
- SDUS和UDEC均表现为高分期（宫外受累）（90% vs. 71%, P=0.28）

TABLE 1. Clinicopathologic and Immunohistochemical Features of Cases of SDUS, Undifferentiated Carcinoma (Undiff), and Dedifferentiated Carcinoma (Dediff)

Case	Age (y)	Diagnosis	Confined to Corpus	FU Time (m)	Last FU Status	BRG1/ SMARCA4	SMARCA2	INI-1/ SMARCB1	Claudin-4	p53	Keratin	EMA	Microsatellite Stability
1	25	SDUS	N	7	DOD	Lost	Lost	Intact	−	WT	−	−	MSS
2	33	SDUS	N	9	DOD	Lost	Lost	ND	−	WT*	−	Focal	MSS
3	34	SDUS	N	1	DOD	Lost	ND	Intact	−	WT	Focal	Focal	MSS
4	29	SDUS	N	4	DOD	Lost	ND	ND	−	WT*	−	ND	MSS
5	58	SDUS	N	43	DOD	ND	ND	ND	−	WT*	−	Focal	MSS*
6	49	SDUS	Y	0	LTFU	Lost	Lost	ND	−	WT*	−	Focal	MSS
7	24	SDUS	N	6	AWD	Lost	Lost	ND	−	WT	−	−	MSS
8	42	SDUS	N	14	DOD	ND	ND	Lost	−	WT*	Multifocal	Multifocal	MSS
9	38	SDUS	N	25	DOD	ND	Lost	ND	−	WT*	−	Focal	MSS*
10	28	SDUS	N	12	DOD	Lost	Lost	ND	−	WT	Rare cells	−	MSS
11	31	SDUS	N	3	DOD	Lost	ND	ND	−	ND	−	Multifocal	ND
12	38	SDUS	NA	0	LTFU	Lost	ND	Intact	−	WT	−	ND	ND
13	57	Dediff	Y	124	NED	Lost	Lost	Intact	+	ND	ND	ND	MSS
14	23	Dediff	N	5	DOD	Lost	Lost	Intact	+	WT*	Focal	Focal	MSS
15	66	Dediff	N	4	DOD	Intact	ND	Intact	−	ND	−	ND	ND
16	60	Dediff	N	2	DOD	Intact	ND	Intact	−	ND	Multifocal	ND	ND
17	64	Dediff	N	2	DOD	Intact	ND	Intact	−	WT	−	Focal	MSS
18	71	Dediff	N	20	DOD	Intact	ND	Intact	+	Mutant*	ND	ND	MSS
19	70	Dediff	N	0	LTFU	Intact	ND	Intact	+	Mutant	Focal	ND	ND
20	59	Dediff	Y	7	NED	Intact	ND	Intact	−	Mutant	−	−	MSS
21	68	Dediff	N	4	NED	Intact	ND	Intact	+	Mutant	Diffuse	Patchy	MSS
22	72	Dediff	N	0	LTFU	Intact	ND	Intact	−	WT	−	Multifocal	MSI
23	66	Dediff	N	1	NED	Intact	ND	Intact	−	ND	Multifocal	ND	MSS
24	69	Dediff	N	0	LTFU	ND	ND	ND	ND	Mutant	Multifocal	ND	ND
25	49	Dediff	N	2	LTFU	ND	ND	ND	ND	WT	−	ND	ND
26	55	Dediff	N	12	NED	ND	ND	ND	ND	ND	ND	ND	MSI (MLH1)
27	55	Dediff	N	29	NED	ND	ND	ND	ND	ND	Focal	ND	MSI (MLH1)
28	73	Dediff	N	8	DOD	ND	ND	ND	ND	WT	Multifocal	ND	MSI (MLH1)
29	68	Dediff	N	1	NED	ND	ND	ND	ND	WT	Focal	Focal	MSI (MLH1)
30	58	Undiff	N	93	NED	Lost	Lost	Intact	−	WT	−	Focal	MSS
31	55	Undiff	N	52	NED	Lost	Lost	Intact	−	WT*	Multifocal	ND	MSI (MLH1)
32	52	Undiff	N	91	DOD	Intact	ND	Intact	ND	WT*	Focal	Focal	MSS*
33	58	Undiff	Y	1	NED	Intact	ND	Lost	+	Mutant	Diffuse	ND	MSS
34	68	Undiff	Y	41	NED	Intact	ND	Intact	+	WT	Multifocal	Diffuse	MSS
35	65	Undiff	N	10	DOD	Intact	ND	Intact	+	Mutant*	−	ND	MSI (MLH1)
36	83	Undiff	Y	17	Alive	Intact	ND	Intact	+	WT	−	Focal	MSS
37	83	Undiff	NA	2	DOD	Intact	ND	Intact	−	Mutant	Focal	ND	MSS
38	59	Undiff	N	0	LTFU	Intact	ND	Intact	−	WT	−	−	MSI
39	77	Undiff	Y	0	LTFU	Intact	ND	Intact	−	WT	−	Focal	MSI
40	72	Undiff	NA	0	LTFU	ND	ND	ND	ND	Mutant	Focal	Focal	ND
41	60	Undiff	N	4	DOD	ND	ND	ND	ND	ND	Focal	ND	MSI (PMS2)

Cases 1 to 5 were previously reported in Kolin et al.[9]

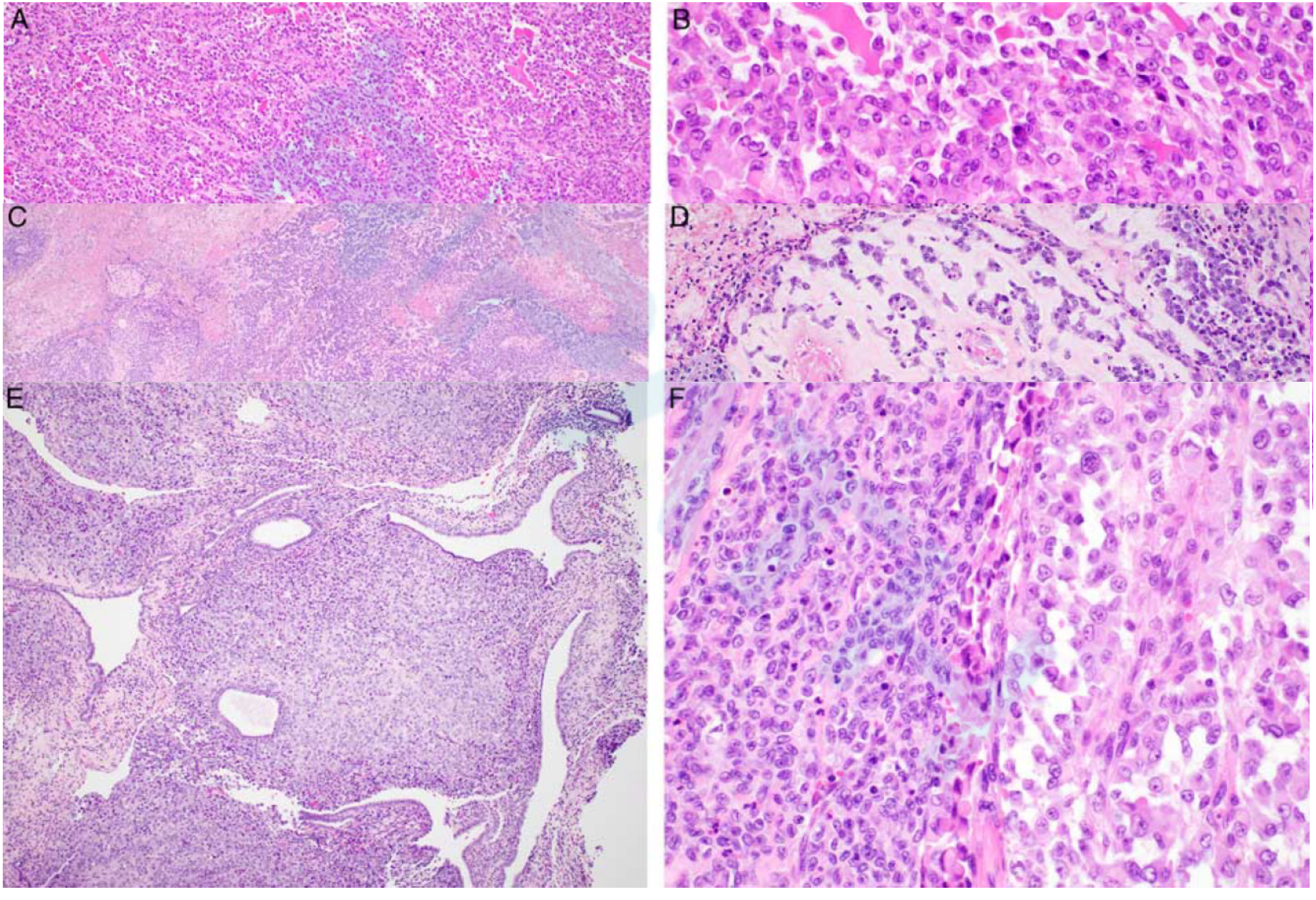
Results denoted by * were determined by MPS, while those without * were determined directly by immunohistochemical staining. The keratin and EMA immunostain details are provided in the supplemental material.

DOD indicates dead of disease; FU, follow-up; LTFU, lost to follow-up; MSS, microsatellite stable; NA, not available; ND, not done; NED, no evidence of disease.

组织结构

- SDUS和UDEC有共同的形态学特征，包括核分裂活跃（平均20/10HPF vs. 27/10HPF,P=0.16）、不典型核分裂增多（45% vs. 40%，P=1.0）、坏死（40% vs. 74%，P=0.12）和淋巴血管侵犯（80% vs. 78%，P=1.0）
- **间质透明化**（55% vs. 12%，P=0.01）和**叶状结构**（36% vs. 0%，P=0.005）均有利于诊断**SDUS**
- SDUS中未见明显的核多形性，但24%UDEC可见明显的核多形性，但这一差异无统计学意义（P=0.15）

SMARCA4-deficient uterine sarcoma



Undifferentiated endometrial carcinomas

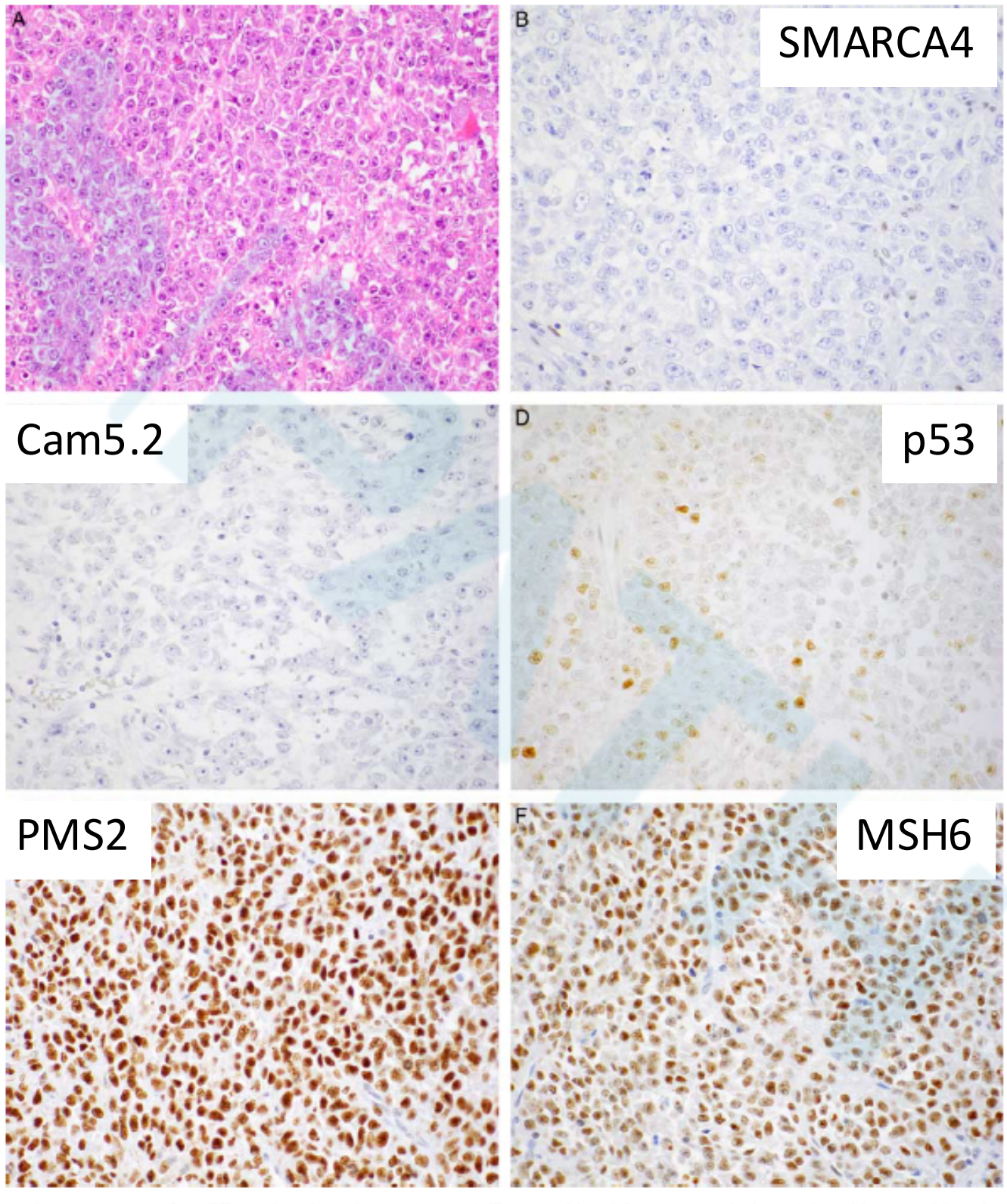


FIGURE 2. Some cases of undifferentiated carcinoma (case 30 illustrated here) have a morphology (A) and immunohistochemical profile which overlaps with SDUS, with (B) SMARCA4 loss, (C) Cam5.2 negativity, (D) wild-type p53 staining, and intact mismatch repair proteins (E, PMS2 and F, MSH6).

Dedifferentiated endometrial carcinomas

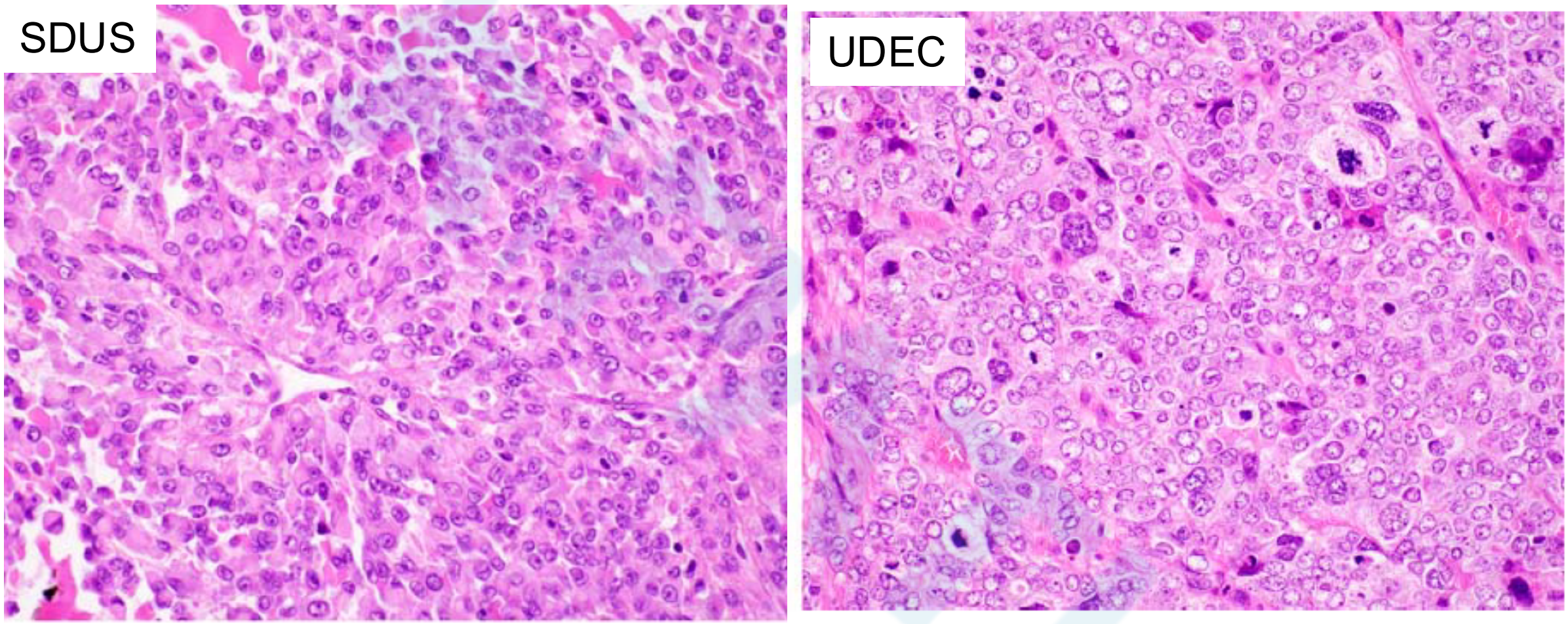


FIGURE 3. A, Dedifferentiated carcinoma is a biphasic tumor composed of a well-differentiated component adjacent to a dedifferentiated component. B, In a subset of cases of UDEC, there is prominent nuclear pleomorphism (compare with Fig. 1B, F).

免疫组化及MPS

- 所有的SDUS都是微卫星稳定的（10/10），而*UDEC*中有34/78（44%）出现一个或多个*错配修复蛋白的表达缺失*（P=0.006）
- 12例SDUS中有10例BRG1/SMARCA4 (n=9)或INI-1/ SMARCB1 (n=1)免疫组化表达缺失，另2例MPS检测到SMARCA4缺失；但UDEC只有11/55 (20%) MARCA4表达缺失
- 所有检测到SMARCA4缺失的肿瘤，包括UDEC和SDUS，都显示了SMARCA2的丢失。
- *TP53突变*（MPS或IHC）在UDEC中很常见（34%），但SDUS并无发现（0%，P=0.03）
- *Claudin-4*仅在UDEC表达（45% vs. 0%，P=0. 01）

- *UDEC*表现出与子宫内膜癌相同的突变类型（*PTEN*、*PIK3CA*、*CTNNB1*、*TP53*）。这些在SDUS中未发现，后者以SMARCA4突变为特征，而其他突变相对较少
- 11/21(52%)UDEC检测到*PTEN*突变，但SDUS均未发现

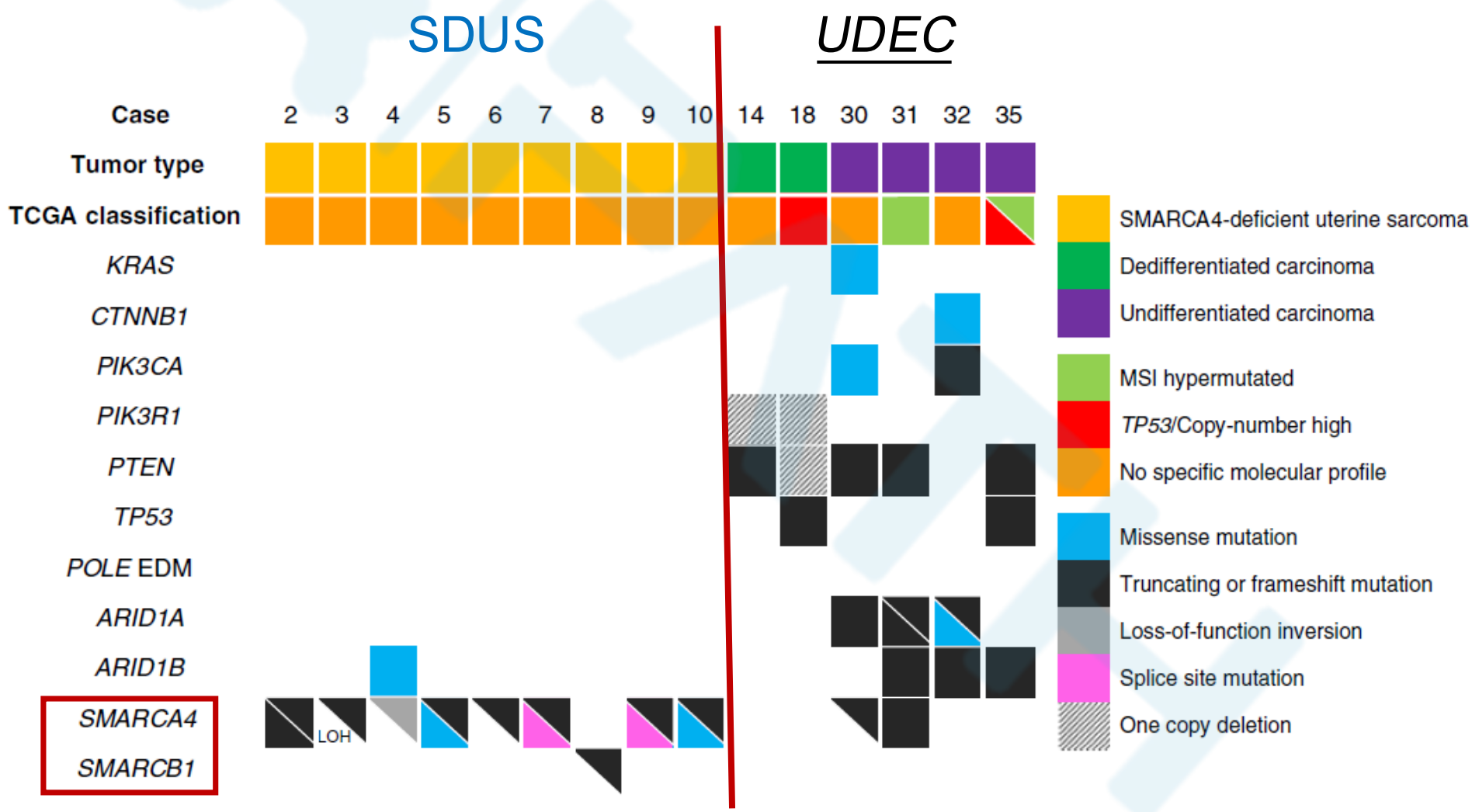


FIGURE 4. Summary of molecular profiling for cases of SDUS (n = 9), dedifferentiated carcinoma (n = 2), and undifferentiated carcinoma (n = 4). SDUS, undifferentiated, and dedifferentiated carcinomas may all have mutations in SWI/SNF components (eg, *SMARCA4*, *SMARCB1*, and *ARID1B*). However, undifferentiated and dedifferentiated carcinomas may also show MSI and mutations in genes such as *TP53*, *PTEN*, *PIK3CA*, features not seen in SDUS. EDM: exonuclease domain mutation. LOH indicates loss of heterozygosity.

- SDUS拷贝数变异(CNV)相对较少（55%的病例无CNV，其余病例仅有很少的CNV）。相比之下，*UDEC的CNV变异更大*（只有16%没有CNV）

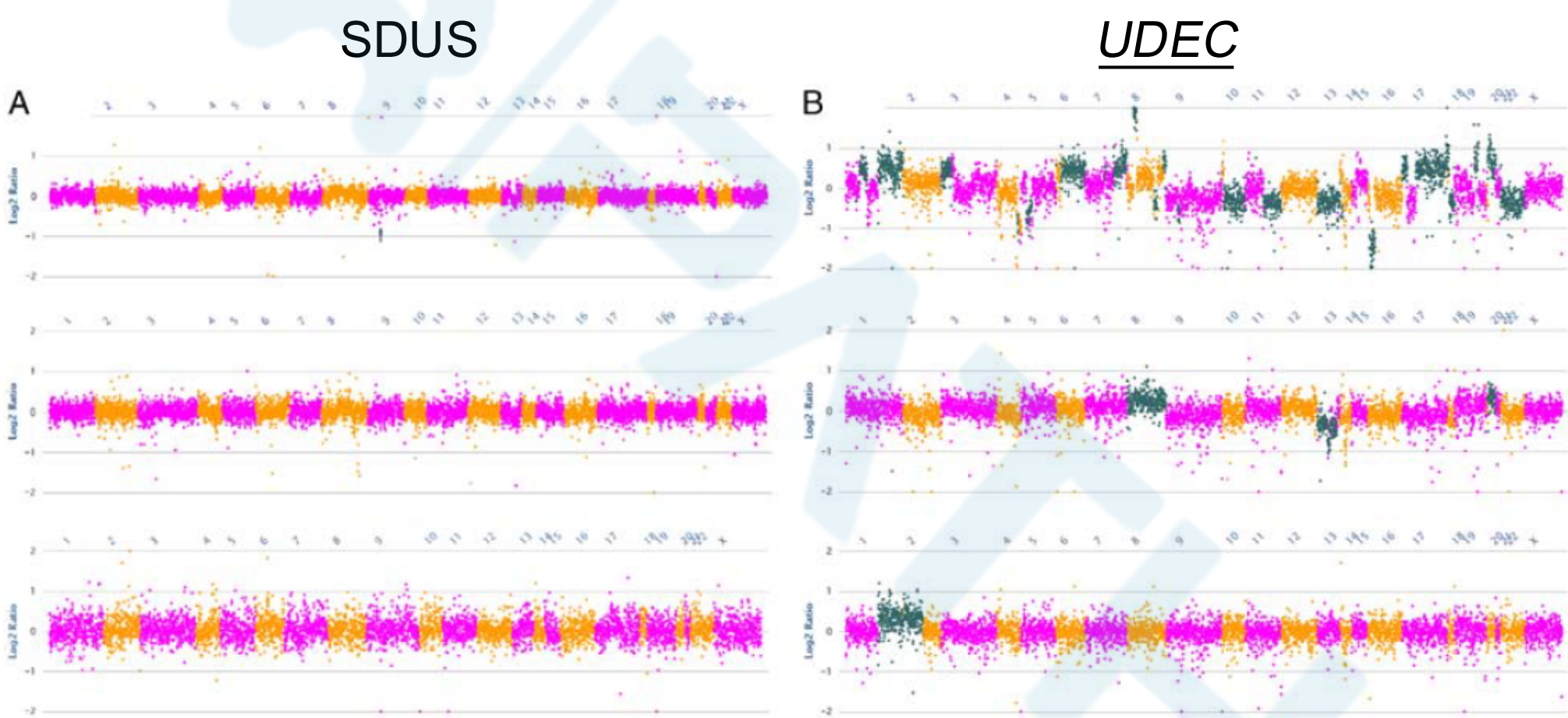


FIGURE 5. Copy number plots of representative cases of SDUS and UDEC. A, SDUS usually shows relatively few copy number alterations, with (from top to bottom): focal loss of *CDKN2A* (case 3), and no copy number changes (cases 6 and 9). B, Cases of UDEC show variable numbers of copy number alterations, depending on their corresponding TCGA subgroup (from top to bottom): case 18, copy-number high; case 35, microsatellite unstable; case 32, copy-number low.

- 疾病特异性生存期(DSS)：SDUS较UDEC显著降低（中位数9个月 vs.中位数36个月，log-rank P=0.01）

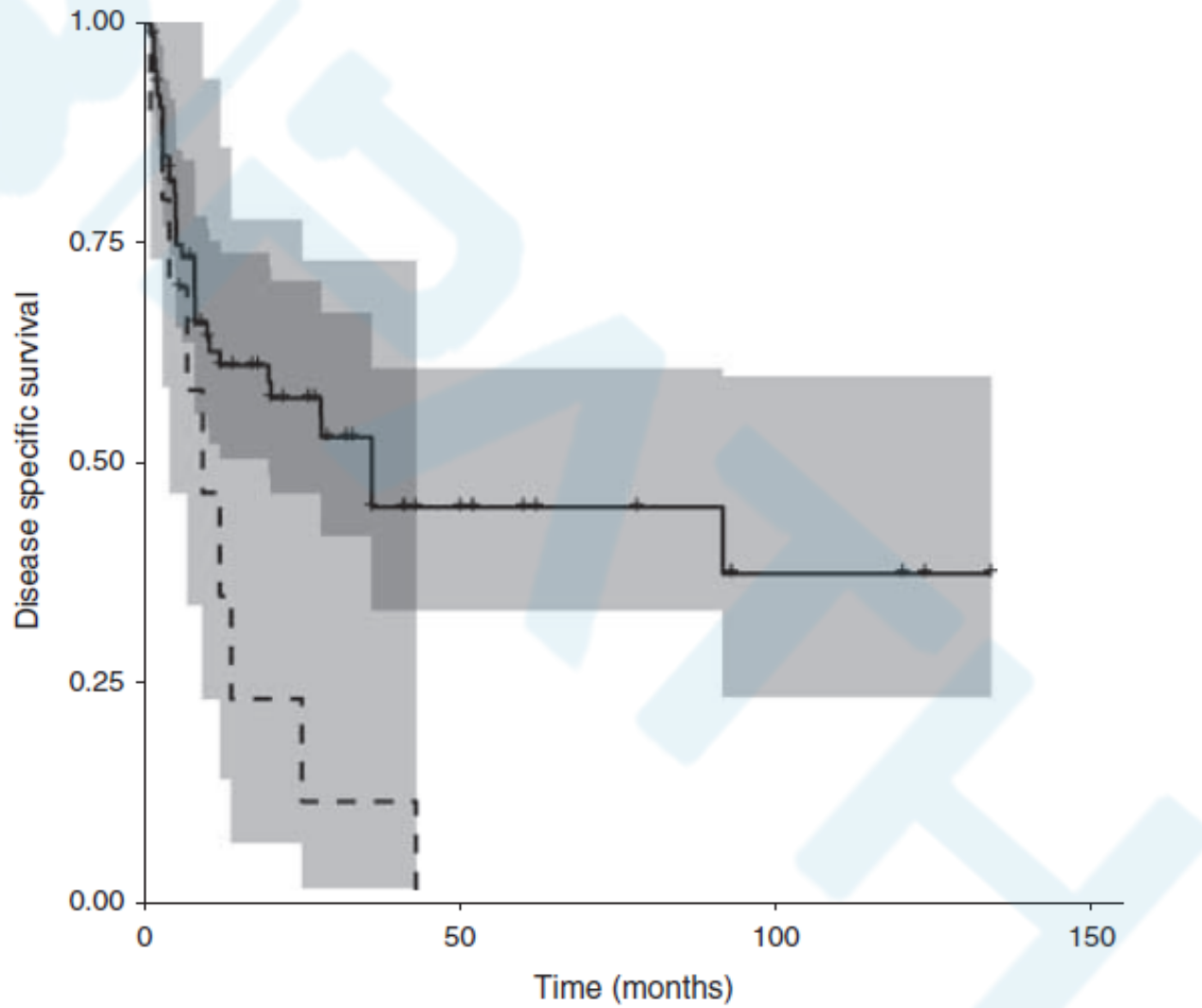


FIGURE 6. Kaplan-Meier survival curve comparing disease-specific survival of SDUS (dashed line) and UDEC (solid line, log-rank $P=0.01$), with 95% confidence intervals.

讨论

UDEC和SDUS形态学

- 相同点：上皮样细胞形态，核分裂活跃，坏死，淋巴血管侵犯。横纹肌样形态在25%UDEC可见，常呈条索状，SDUS也可见到这些特征。
- 不同点：24%UDEC高倍镜下可见明显的细胞多形性。而SDUS虽然表现出明显的异型性，但细胞形状和细胞核大小没有明显的变化。部分SDUS可见叶状结构，但UDEC没有观察到这种生长模式。
- 因此，局灶性和模糊的叶状结构或间质透明变有助于诊断SDUS，而显著的细胞多形性更支持UDEC。

UDEC和SDUS免疫表型

- 相同点：角蛋白通常仅局部表达，ER、PR和PAX8阴性
- 不同点：claudin-4显著阳性可排除SDUS的诊断，但是，SDUS和UDEC均可以claudin-4阴性。
- CK18是未分化癌中最敏感的细胞角蛋白，高达86%的病例可呈局灶性阳性，但SDUS表达情况尚未研究。

UDEC和SDUS分子表型

- 相同点：SDUS (always) 和UDEC (often，20%)均显示出SWI/SNF基因SMARCA4或SMARCB1的失活。
- 不同点：UDEC经常显示MSI和PTEN，TP53，PIK3CA等子宫内膜癌常见的分子改变；而SDUS则缺乏这些改变，总是SMARCA4缺失；可用P53，MMR ，PTEN，SMARCA4等免疫组化进行鉴别。
- 故，从分子角度来看，UDEC和SDUS是完全不同的肿瘤实体。

区分SDUS和UDEC的重要性

- 首先，尽管两种肿瘤预后均较差，但SDUS的DSS更差。
- 第二，SDUS患者可能存在SMARCA4胚系突变--与横纹肌样肿瘤易感综合征2相关，非典型畸胎样/横纹肌样瘤和SCCOHT发病风险增加。确定携带者有助于对其家庭成员进行检测和适当的筛查。
- 第三，包括PD-L1、EZH2和CDK4/6抑制剂在内的靶向治疗在SCCOHT等由SWI/SNF复合物突变驱动的恶性肿瘤治疗中发挥作用，相同的治疗方法可能对SDUS有价值。

SDUS其他鉴别诊断

- **SCCOHT，大细胞型**

  SDUS发生于子宫内，临床表现主要为宫颈肿块或阴道出血，可能累及双侧卵巢，WT1、角蛋白阴性；SCCOHT通常是一个大的(平均15厘米)的单侧卵巢肿块，伴高钙血症，临床表现以腹痛腹胀为主，EMA、CAM5.2、WT1及CD10阳性；当卵巢有明显的肿瘤时，应首先考虑SCCOHT大细胞变异型。

- **上皮样肉瘤**

  SDUS发生在子宫内，侵袭性高，进展快，CD34阴性，SMARCA4缺失；而近端型上皮样肉瘤通常发生在腹股沟区或外阴，病程较长，局部复发频繁，大约一半病例CD34阳性，SMARCB1（INI1）的丢失。

- **上皮样平滑肌肉瘤和PEComa**

  这二者常表现出明显的核多形性，均表达平滑肌标记物，而且PEComas对HMB-45、melanA阳性。SDUS细胞形态通常比较单一，平滑肌和黑素细胞分化的标记物均为阴性，SMARCA4缺失。

结论

- SDUS应作为一种独立的临床病理实体，与UDEC、未分化子宫肉瘤等区别开。
- SDUS相较于UDEC发病年龄更年轻，预后更差。
- 二者都具有横纹肌样形态、核分裂活跃、坏死、淋巴血管侵犯等共同形态特点，但**叶状结构或间质透明变更倾向SDUS**，而**显著的细胞多形性更支持UDEC。**
- 一组IHC包括**CK18 、claudin-4、MMR、p53、 PTEN ， BRG1/ SMARCA4**和**INI-1/SMARCB1**，可以在绝大多数情况下区分SDUS和UDEC（敏感性100%，特异性92%），一小部分可能需要进行分子检测。
- 识别SDUS不仅对预后很重要，而且对胚系检测和靶向治疗方案也有重要意义。
- 活检标本难以区分时不一定需要明确的诊断，可以作出描述性诊断，如“恶性上皮样肿瘤”，并提出鉴别诊断。

感谢聆听

Table 3 Comparison of clinicopathologic features of SWI/SNF complex-deficient tumors

From: SMARCA4-deficient undifferentiated uterine sarcoma (malignant rhabdoid tumor of the uterus): a clinicopathologic entity distinct from undifferentiated carcinoma

	Age	Location	Main molecular abnormality	Germline association	Prognosis	Non-germline risk factors
Malignant rhabdoid tumor [31, 32]	Usually infants <1 year, rarely adolescents and adults	Kidney, liver, head and neck	*SMARCB1* in 95%, rare cases with *SMARCA4*	*SMARCB1* deletion in 15–30%	Poor; 31% of patients survive 1 year	Low birthweight, preterm birth
Small cell carcinoma of the ovary, hypercalcemic type [1,2,3,4, 33,34,35]	Mean 24 years (range 14 months–71 years)	Ovary	*SMARCA4*	*SMARCA4* mutation in 8%-50%	Poor; almost all patients greater than stage 1A die from disease; 10–20% overall survival	None
Atypical teratoid/rhabdoid tumor [32, 36,37,38]	Usually under 3 years, rarely adolescents and adults	CNS	Usually *SMARCB1*, rarely *SMARCA4*	*SMARCB1* mutation in 35%	Poor; median survival 8 months	Low birthweight, increased maternal age, higher parental socioeconomic status
Proximal-type epithelioid sarcoma [39]	Median 40 years (range 13–80 years)	Inguinal region, thigh, vulva	*SMARCB1*	None	Local recurrences common; median survival 6 years	History of trauma in some cases
SMARCA4-deficient thoracic sarcoma [7, 40]	Median 39 years (27–82 years)	Thorax	*SMARCA4* mutations and LOH; *TP53* mutations	None	Poor; median survival 7 months	Heavy smoking
Undifferentiated endometrial carcinoma [14, 20]	Mean 59 years (range 40–69 years)	Endometrium	*KRAS, PTEN, CTNNB1*, MMR proteins, *ARID1A SMARCA4, SMARCB1*	None	Stage dependent; survival of months to years	Unknown
SMARCA4-deficient uterine sarcoma	Mean 36 years (range 25–58 years)	Uterus	*SMARCA4*	Unknown	Poor; average survival ~6 months	Unknown, possibly radiation therapy