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Molecular Profiles of Mixed Endometrial Carcinoma

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混合性子宫内膜癌（MEC）

- 定义
- 由两种或多种不同组织学类型子宫内膜癌构成的癌，其中至少包含一种Ⅱ型子宫内膜癌，比例超过5%。
- ICD-O 编码
- 混合细胞性腺癌 8323/3

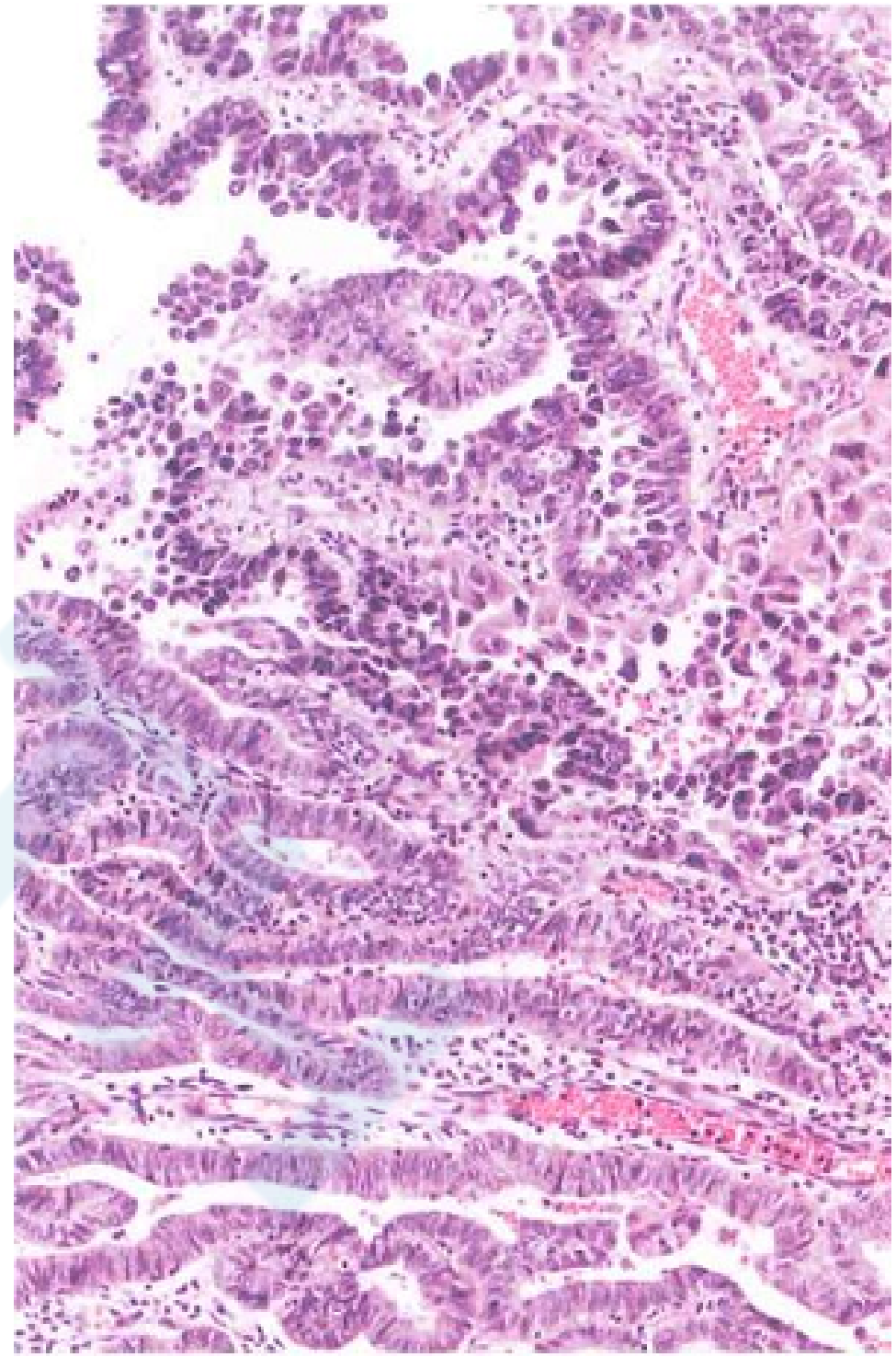


图 5.08 混合性癌，浆液性癌与子宫内膜样癌混合。

子宫内膜癌分型

Ⅰ型：子宫内膜样癌(EC)

绝经后女性雌激素浓度高、多囊卵巢综合征，产雌激素的卵巢肿瘤；有子宫内膜癌家族史、Lynch 综合征等。

Ⅱ型：浆液性癌(SC) 透明细胞癌(CC)

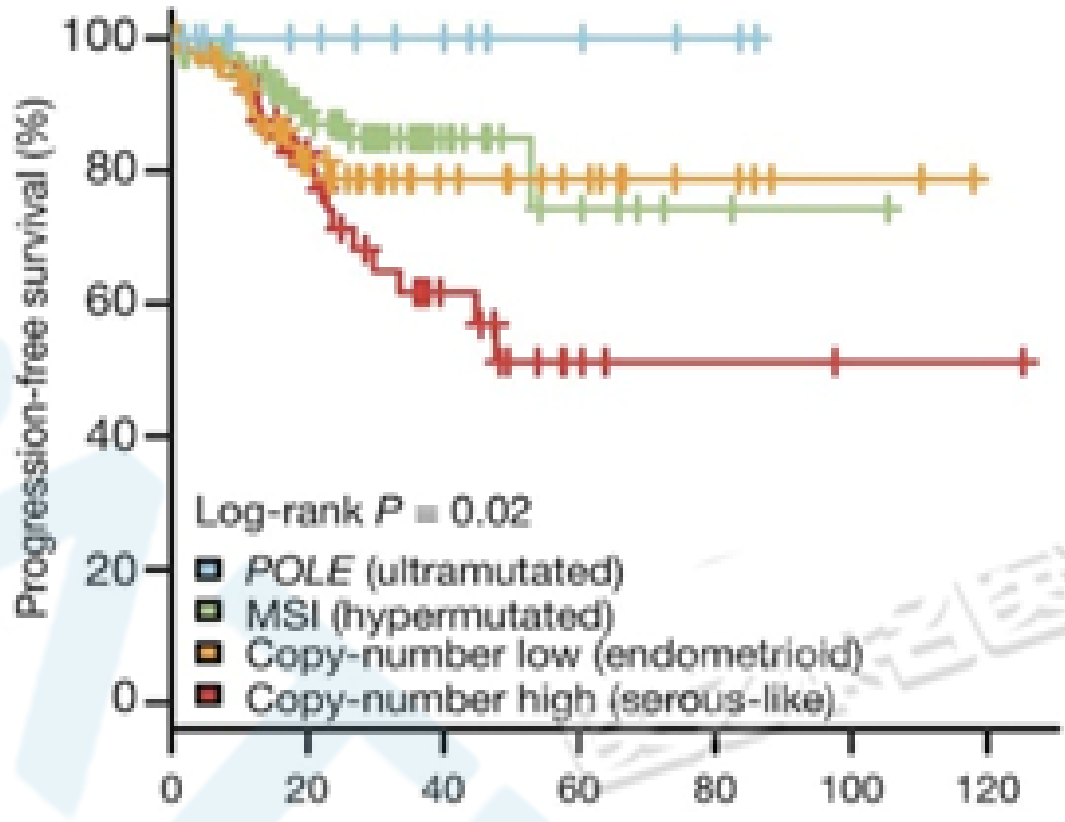
多产妇、吸烟者、输卵管结扎术后、有乳腺癌病史和/或他莫昔芬服用史等。

子宫内膜癌分型

	Ⅰ型	Ⅱ型
免疫组化	ER PR Vim bcl-2	P53 P16 KI-67 (Napsin-A）
遗传学特征	PTEN 突变或失活 PIK3CA 、PIK3R1 、ARID1A、KRAS 和 TP53 突变； 微卫星不稳定性最常见的原因是MLH1基因启动子超甲基化； POLE基因突变，导致超高频突变。	SC: TP53、PIK3CA、FBXW7和 PPP2R1A； BRCA1/2 胚系突变。 CC: PTEN 和 TP53 、PIK3CA，无 ARID1A 突变。

子宫内膜癌分子分型

1. POLE基因突变和超突变表型，预后很好；
2.微卫星不稳定型（MSI），高突变型；
3.低拷贝型（CN-low），
4.高拷贝型（ CN-high），主要为高度恶性浆液性癌，P53突变，预后差。



- POLE突变组预后非常好，90个月随访期患者100%生存；高拷贝组预后差；MSI和低拷贝组的生存率无区别
- 综合分析镜下形态和分子特征是预测患者预后的最佳方法

参考姜彦多教授《子宫内膜癌病理诊断》课件

引言

- MEC的诊断是基于形态学和免疫表型。
- 在新的分子分型的标准下，MEC应该归属哪一类肿瘤？
- 本研究目的就是确定肿瘤的单个成分的分子基础，以更好的理解潜在的致癌机制。

材料与方法

- 病例选择：8例MEC
- 1.所有病例均有3名妇科病理学专家进行复查；
- 2. 不明确的、未分化的以及有恶性间质成分的病例都被排除；
- 3.所有病例均局限于2种组织学亚型（EC、SC和/或CC）；
- 4.根据宏观解剖的可行性选择病例，选择不同的肿瘤区域，来最小化交叉污染的风险。

结果

TABLE 1. Clinicopathologic Characteristics

Case No.	Age (y)	Diagnosis	%	Histologic Description	Unexpected IHC	FIGO Stage	Treatment	Clinical Follow-up, Duration
1 (3*)	58	G2 EC/SC	75% EC 25% SC	EC: glandular, 10% solid; grade 1-2 nuclei, smooth luminal borders SC: papillary, detached cell clusters, slit-like spaces, grade 3 nuclei	p16: diffusely positive in both ER/PR: strongly positive in SC Napsin A: weakly positive in both	IIIC1	TAHBSO/LND Chemotherapy (6 cycles)	8 mo PFS followed by recurrent disease, then lost to follow-up
2 (5*)	81	G2 EC/SC	90% EC 10% SC	EC: glandular, 10%-20% solid, grade 2 nuclei, intraglandular necrosis; focal squamous differentiation; associated hyperplasia SC: colonizing hyperplasia adjacent to EC; hyperchromatic nuclei, pleomorphism, budding, and micropapillae	p16: diffusely positive in both	IC	TAH/BSO/LND Chemotherapy Pelvic radiation	NED from MEC at 4 y Subsequent stage IV NSCLC, persistent
3 (6*)	70	G3 EC/SC	20% EC 80% SC	EC: glandular, ~60% solid, grade 1-2 nuclei, low mitotic count; predominantly polypoid SC: grade 3 nuclei, prominent nucleoli, increased mitoses, papillary and glandular architecture; nonpolyp and deeply invasive	p53: null in both p16: diffusely positive in both	IIIC2	TLHBSO/LND Chemotherapy	11 mo PFS followed by recurrent disease
4 (7*)	52	G1 EC/SC	30% EC 70% SC	EC: glandular, focal MELF pattern, lymphocytic inflammation SC: arising in LUS, papillary and solid growth; pleomorphic nuclei, prominent nucleoli, high mitotic rate	Expected pattern	II	TLHBSO/LND Chemotherapy (6 cycles) Pelvic radiation	NED (6 y) Subsequent breast cancer
5 (11*)	83	SC/CC	80% SC 20% CC	SC: glandular with micropapillae and hobnailing, grade 3 nuclei, numerous mitoses, bizarre/pleomorphic cells CC: papillary and solid, clear cytoplasm, defined cell borders; deeply invasive	p53: diffusely positive in both p16: negative in CC	IIIC1	TAHBSO/LND Chemotherapy (6 cycles)	NED (11 y)

结果

6 (8*)	52	G2 EC/ CC	30% EC 70% SC	EC: glandular, 15%-20% solid, some villoglandular growth, grade 1-2 nuclei, smooth luminal borders CC: eosinophilic variant, associated psammomatous calcification, prominent nucleoli, abundant cytoplasm, extensive LVI	Expected pattern	IIIC2	TLHBSO/LND/ omentectomy Chemotherapy (6 cycles) Vaginal cuff brachytherapy	Recurrence at 7 mo in supraclavicular LN NED since (6 y)
7 (14*)	71	G3 EC/ CC	70% EC 30% CC	EC: glandular, > 50% solid, grade 1-2 nuclei, stratified, background hyperplasia CC: solid, clear cytoplasm, defined cell borders, no stratification	Napsin A: negative in CC	III3C1	TAHBSO/LND Chemotherapy (6 cycles) Pelvic radiation	NED (8 y)
8 (15*)	66	G2 EC/ CC	60% EC 40% CC	EC: glandular, ~15% solid, smooth luminal borders, foci of squamous differentiation CC: tubulocystic, defined cell borders, clear cytoplasm	ER/PR: positive foci in CC	III3A	TAHBSO Chemotherapy Pelvic radiation	Follow-up at OSH NED at treatment end (9 mo)

*Case number in previous publication for cross-referencing.[7]

Please note, case 6 (prior case 8) has been reclassified as a mixed EC/CC case in this study based on the previous and current results.

ER indicates estrogen receptor; G, grade; LND, lymph node dissection; LUS, lower uterine segment; LVI, lymphovascular invasion; MELF, microcystic, elongated, and fragmented; NED, no evidence of disease; NSCLC, non–small cell lung cancer; OSH, outside hospital; PFS, progression-free survival; PR, progesterone receptor; TAHBSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy; TLHBSO, total laparoscopic hysterectomy with bilateral salpingo-oophorectomy.

结果

TABLE 2. Results of Targeted Sequencing in MECs

Case No.	EC Only	Shared Mutations	SC Only
1	No additional	ARID1A, NFE2L2, PIK3CA$_a$, PIK3CA$_b$, PTEN$_a$, PTEN$_b$	POLE, PPP2R1A
2	No additional	ARID1A*, CTNNB1, PIK3CA, PTEN, TP53$_a$, PPP2R1A	TP53$_b$
3	MYC amp	TP53, ERBB2, PPP2R1A	ARID1A, POLE
4	PIK3CA$_a$, FBXW7, RAD50, NF1	ARID1A, MSH6*†, KIT*†	PIK3CA$_b$, DDR2, MAP2K1, TP53$_a$, TP53$_b$, ERBB2, SMARCA4
	CC Only	**Shared Mutations**	**SC Only**
5	No additional	RAF1, FBXW7, MYC amp, TP53*, PPP2R1A	PIK3CA, PTEN, NF1, CCNE1
	EC Only	**Shared Mutations**	**CC Only**
6	PIK3CA, PTEN, FGFR2	MET*	No additional
7	FGFR2, NF1, PIK3CA$_b$	NFE2L2, PIK3CA$_a$, KIT, PTEN	No additional
8	FGFR2	ARID1A, NFE2L2, PIK3CB, RAD50, PTEN$_a$, PTEN$_b$, ERBB3	No additional

The center column shows gene mutations that were shared between components of the MECs. The left and right columns show gene mutations limited to each component, respectively.

*Potential germline mutation.

†Low coverage.

讨论

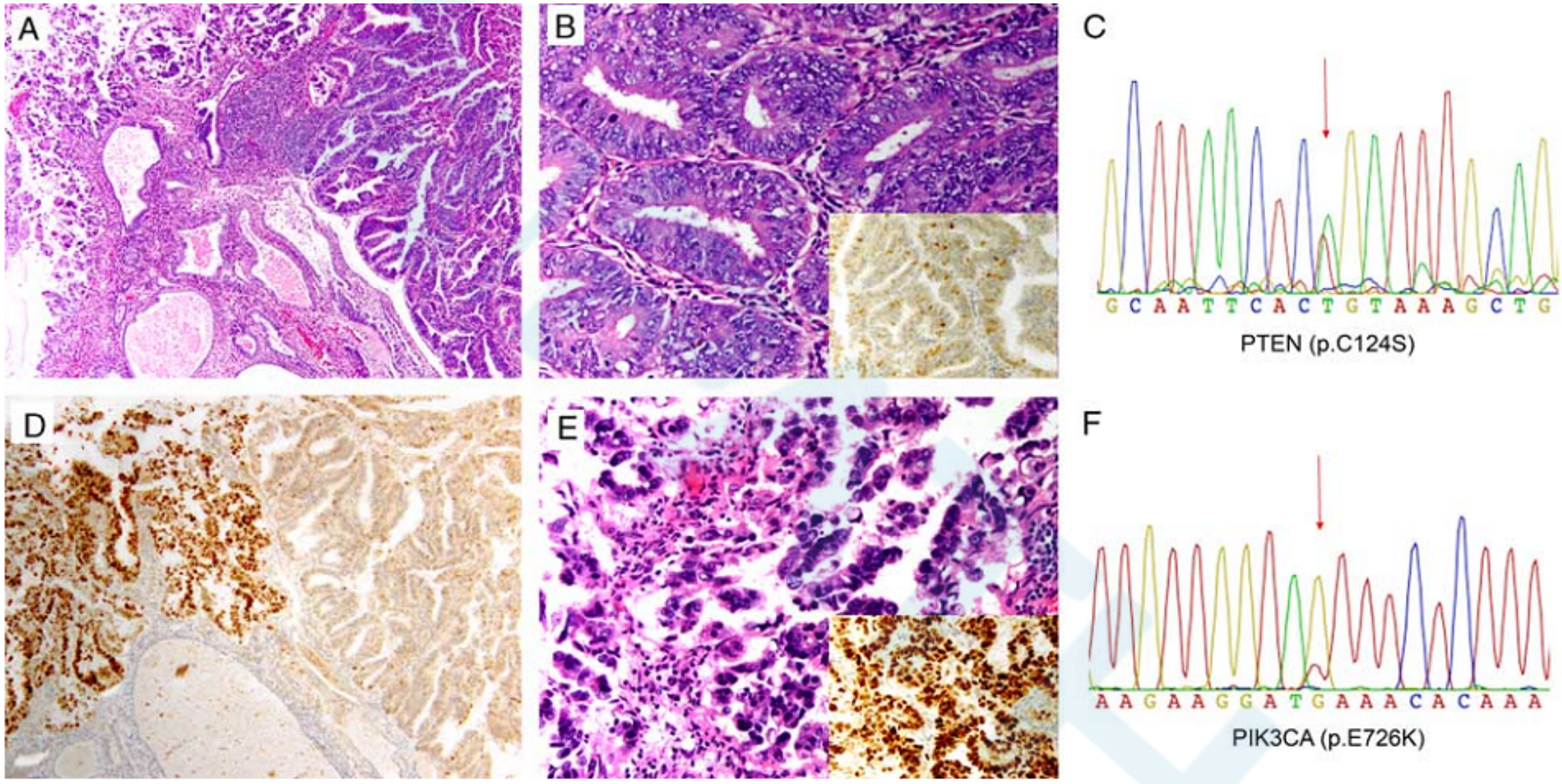


FIGURE 1. Case #2, mixed EC/SC. Sequencing showed that the EC and SC shared a TP53 mutation while the SC possessed an additional TP53 mutation. A, Low-power magnification of EC (right) and SC (left) components. The EC component (B, high power) displayed a wild-type immunostaining pattern for p53 (D, right; B inset) while the SC (E, high power) displayed a strong and diffuse staining pattern for p53 (D, left; E, inset). Sanger sequencing confirmed shared *PTEN* (p.C124S) and *PIK3CA* (p.E726K) mutations (C, F, respectively).

2	No additional	ARID1A*, CTNNB1, PIK3CA, PTEN, $TP53_a$, PPP2R1A	$TP53_b$

讨论

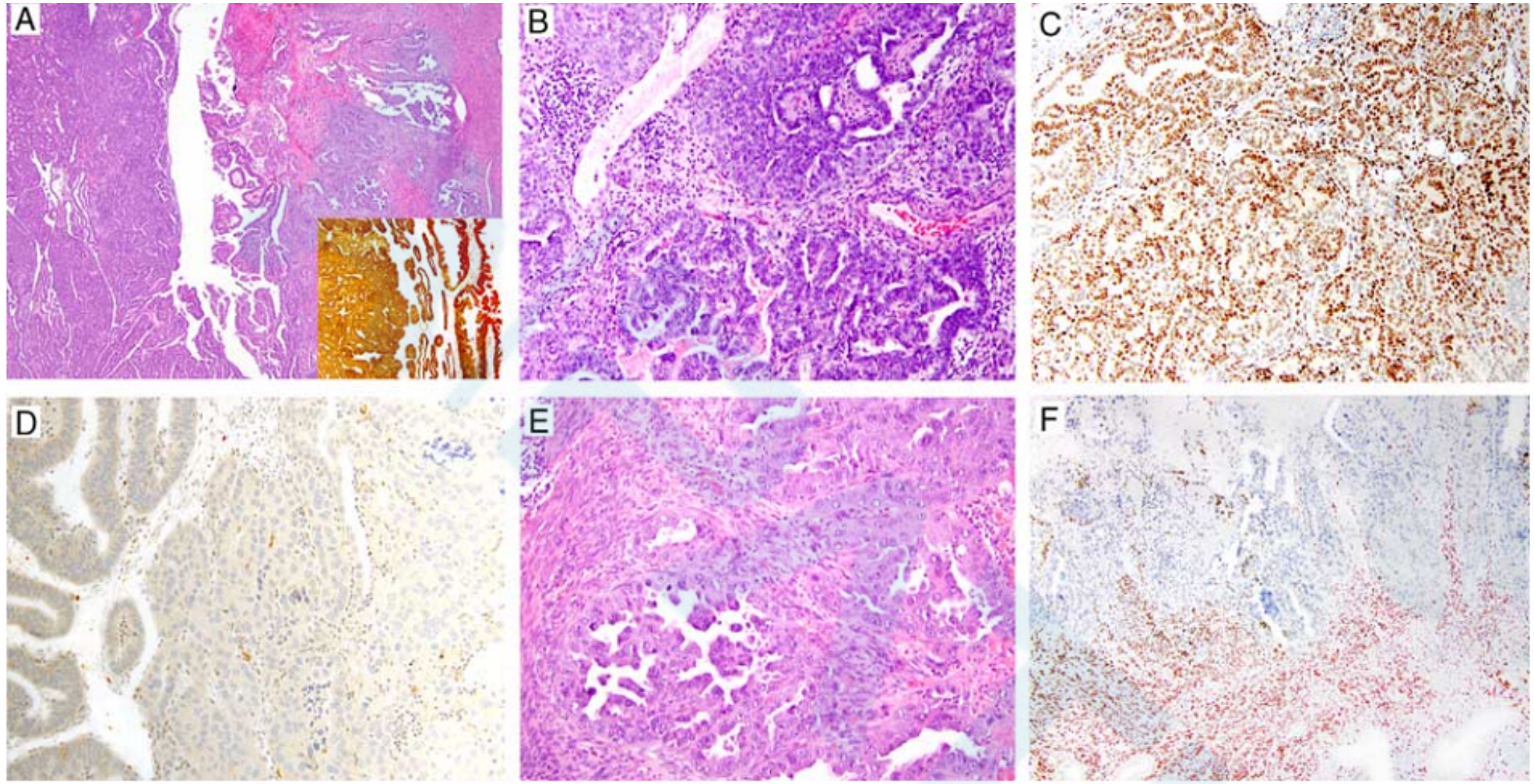


FIGURE 2. Case #3, mixed EC/SC. The EC component was predominantly polypoid, while the SC component was deeply invasive (A—EC on left, SC on right; B, E—high power EC and SC, respectively). p16 was diffusely positive in both components (A, inset) and both components showed a null p53 staining pattern (D—EC on left, SC on right). Immunostaining for ER showed diffusely positive staining in the EC component (C) and negative staining in the SC (F).

3 (6*)	70	G3 EC/ SC	20% EC 80% SC	EC: glandular, ~60% solid, grade 1-2 nuclei, low mitotic count; predominantly polypoid SC: grade 3 nuclei, prominent nucleoli, increased mitoses, papillary and glandular architecture; nonpolyp and deeply invasive	p53: null in both p16: diffusely positive in both	IIIC2	TLHBSO/LND Chemotherapy	11 mo PFS followed by recurrent disease

3	MYC amp	TP53, ERBB2, PPP2R1A	ARID1A, POLE

讨论

- 病例4（EC/SC）中有一个共享的MSH6突变(微卫星不稳定性肿瘤);
- 本例中仅SC成分中出现了TP53的突变（乘客突变）;
- 在SC成分中还发现了潜在靶向基因DDR2、 MAP2K1和ERBB2的激活突变，以及在去分化子宫内膜癌亚群中发现的功能缺失的SMARCA4突变，然而该病例并没有典型的去分化外观。

4 (7*)	52	G1 EC/ SC	30% EC 70% SC	deeply invasive EC: glandular, focal MELF pattern, lymphocytic inflammation SC: arising in LUS, papillary and solid growth; pleomorphic nuclei, prominent nucleoli, high mitotic rate	Expected pattern	II	TLHBSO/LND Chemotherapy (6 cycles) Pelvic radiation	NED (6 y) Subsequent breast cancer	
4		PIK3CA$_a$, FBXW7, RAD50, NF1		ARID1A, MSH6*†, KIT*†					PIK3CA$_b$, DDR2, MAP2K1, TP53$_a$, TP53$_b$, ERBB2, SMARCA4

讨论

- 多项研究强调了分子分类优先的顺序 ，因为MMR缺失、POLE和/或TP53异常可能在同一个肿瘤中共存，独立的将患者置于不同的危险分层组。
- 我们的研究组中，4例TP53突变的病例中，有2例（一个POLE、一个MMR缺失）以这种方式分层将会被置于较低的风险类别。然而，这些患者中至少有一个在一年内死于疾病（病例3POLE），MSH6缺失的病例4无病生存6年，但发展了乳腺癌。
- 这强调了在混合肿瘤中的肿瘤分类可能是一个独特的挑战，需要分别对这两种成分进行排序，以确保准确的患者危险分层和治疗。

3	MYC amp	TP53, ERBB2, PPP2R1A	ARID1A, POLE
4	PIK3CA$_a$, FBXW7, RAD50, NF1	ARID1A, MSH6*†, KIT*†	PIK3CA$_b$, DDR2, MAP2K1, TP53$_a$, TP53$_b$, ERBB2, SMARCA4

EC/CC3例病例中，EC成分均单独发生FGFR2的突变。

(1)FGFR的突变在10%-16%的子宫内膜癌中检测到，特别是子宫内膜样癌，显示与低级别的组织学相关;

- (2)FGFR突变可能与子宫内膜样癌的不良预后和较短的生存期相关。
- (3)FGFR作为潜在治疗靶点的可能性已经被提及，有研究显示了dovotinib的临床活性。

CC Only	Shared Mutations	SC Only
No additional	RAF1, FBXW7, MYC amp, TP53*, PPP2R1A	PIK3CA, PTEN, NF1, CCNE1
EC Only	**Shared Mutations**	**CC Only**
PIK3CA, PTEN, FGFR2	MET*	No additional
FGFR2, NF1, PIK3CA$_b$	NFE2L2, PIK3CA$_a$, KIT, PTEN	No additional
FGFR2	ARID1A, NFE2L2, PIK3CB, RAD50, PTEN$_a$, PTEN$_b$, ERBB3	No additional

- 在EC/CC组没有显示TP53的突变，而SC/CC病例则有TP53的共享突变，并且共享了很多与SC相关的经典突变，而透明细胞成分没有额外的突变。这可能代表浆液性成分的遗传进展，但透明细胞变的区域也可能代表了终端分化现象，即没有额外的突变发生。苗勒氏肿瘤中的透明细胞分化，仍然是一个谜。

CC Only	Shared Mutations	SC Only
No additional	RAF1, FBXW7, MYC amp, TP53*, PPP2R1A	PIK3CA, PTEN, NF1, CCNE1
EC Only	**Shared Mutations**	**CC Only**
PIK3CA, PTEN, FGFR2	MET*	No additional
FGFR2, NF1, PIK3CA$_b$	NFE2L2, PIK3CA$_a$, KIT, PTEN	No additional
FGFR2	ARID1A, NFE2L2, PIK3CB, RAD50, PTEN$_a$, PTEN$_b$, ERBB3	No additional

讨论

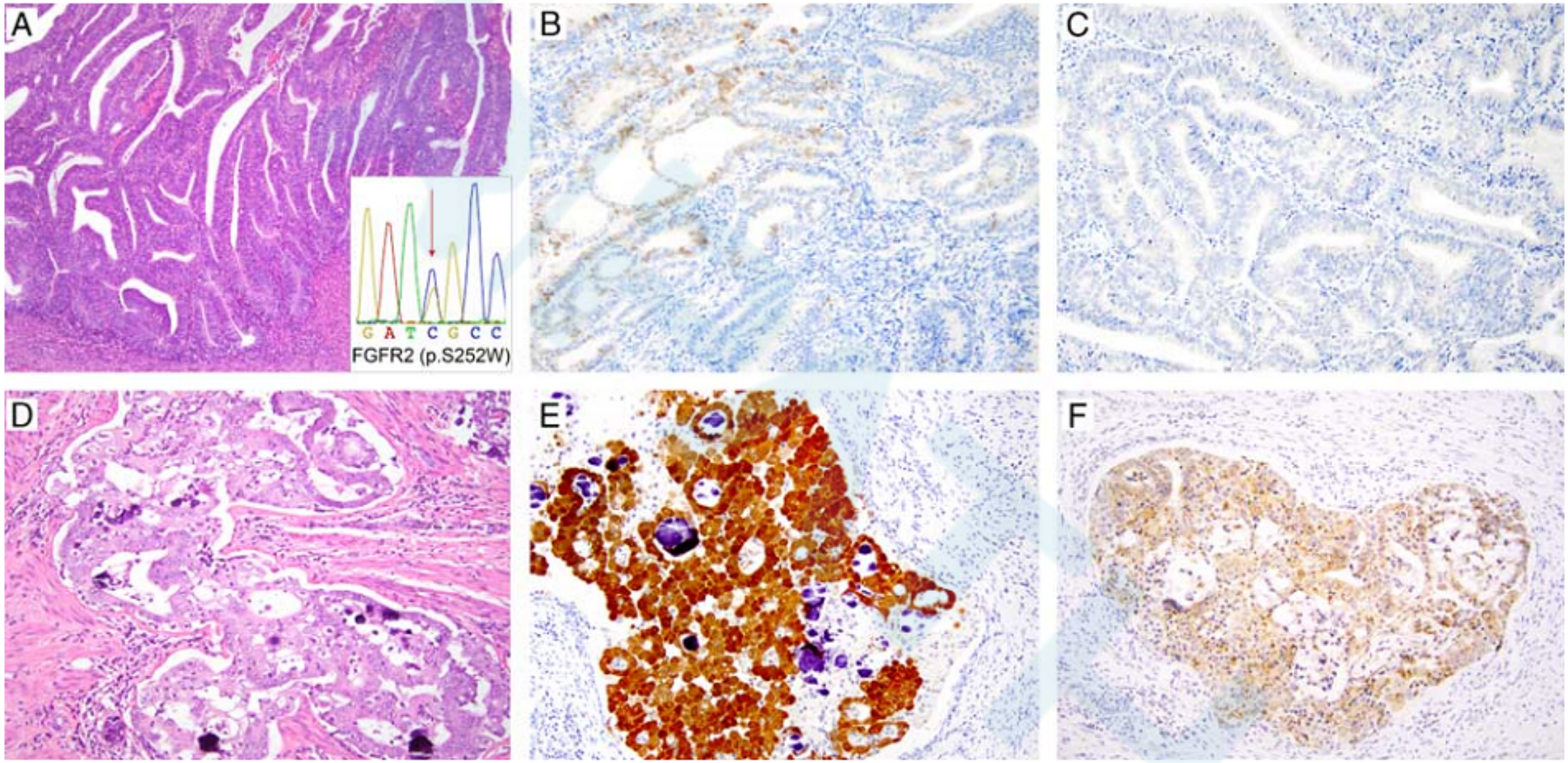


FIGURE 3. Case # 6, mixed EC/CC. The EC component (A) showed patchy/focal p16 (B) and negative Napsin A staining (C). In addition to the shared *MET* (p.E168D) mutation, Sanger sequencing also confirmed a unique *FGFR2* (p.S252W) mutation in the EC (A, inset). The SC component (D) showed a diffusely positive p16 (E) as well as positive Napsin A staining (F).

6	PIK3CA, PTEN, FGFR2	MET*	No additional

讨论

- 另一个有趣的特性是这些肿瘤中可能发生的形态拟态，有一些病例有典型的组织学形态，却具有意想不到的分子特征。

- 例如EC成分表现出共享的SC分子突变，相反也有一些病例，SC的形态学却具有EC的超突变和高突变特征，例如前面的POLE和MSH6病例。
- 最好的例子是病例6，它显示了类似SC形态的区域，但没有SC的突变，并且在免疫组化上也准确的归为EC/CC病例。

结论

- 1. 所有的MECs在两种成分中都有共享的突变，但在不同病例的肿瘤成分中没有表现出相同的分子特征。
- 2. 肿瘤开始作为单一的克隆，演进分为两个途径（1）肿瘤进展，只有一个成分获得额外的突变；（2）肿瘤分化，肿瘤成分都有共享的突变，每个成分都获得额外的突变。
- 3. 要小心肿瘤的形态拟态的陷阱，选择合适的辅助检查帮助诊断。

- MEC仍然是一个具有挑战性的实体肿瘤，我们一直在不断了解更多的这些肿瘤的发生机制，和它们在子宫内膜癌分类中的最新进展。

THANK YOU

谢谢观看