

SMARCA4-deficient Sinonasal Carcinoma

*A Series of 10 Cases Expanding the Genetic Spectrum of
SWI/SNF-driven Sinonasal Malignancies*

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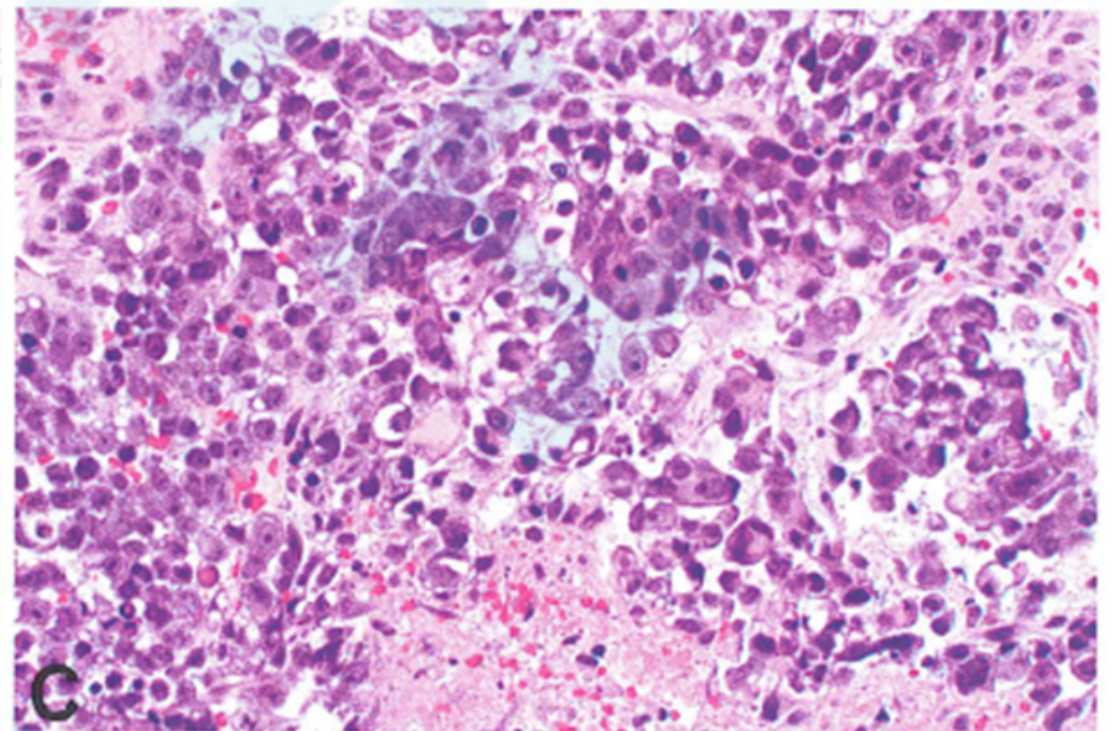
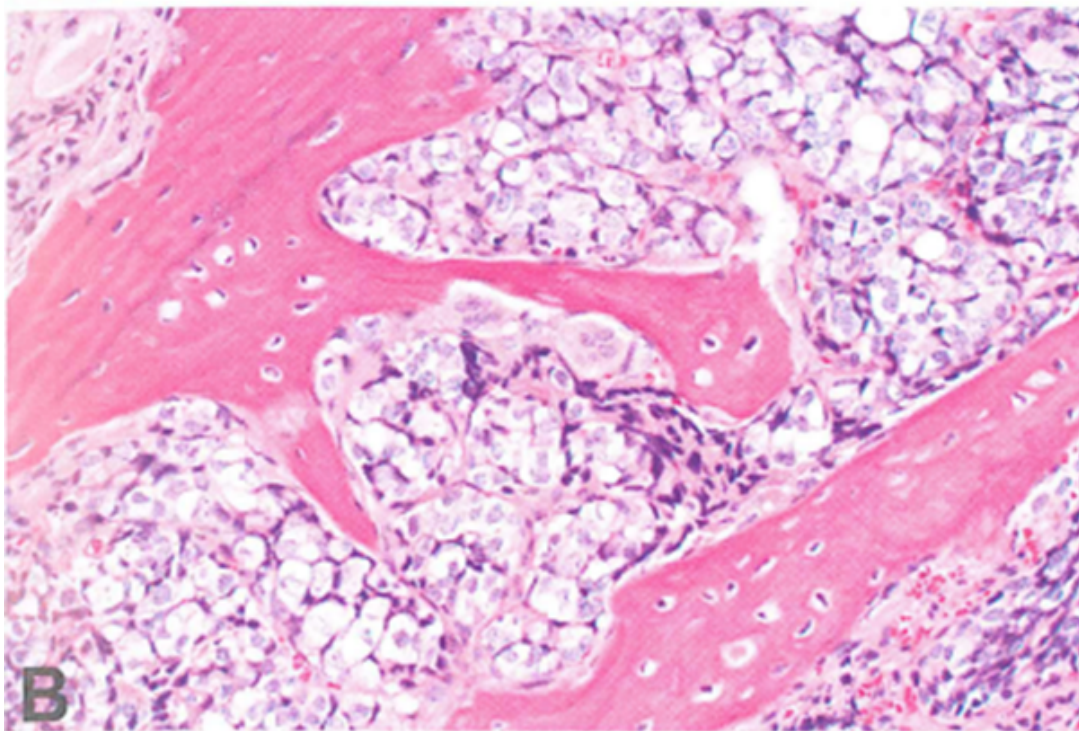
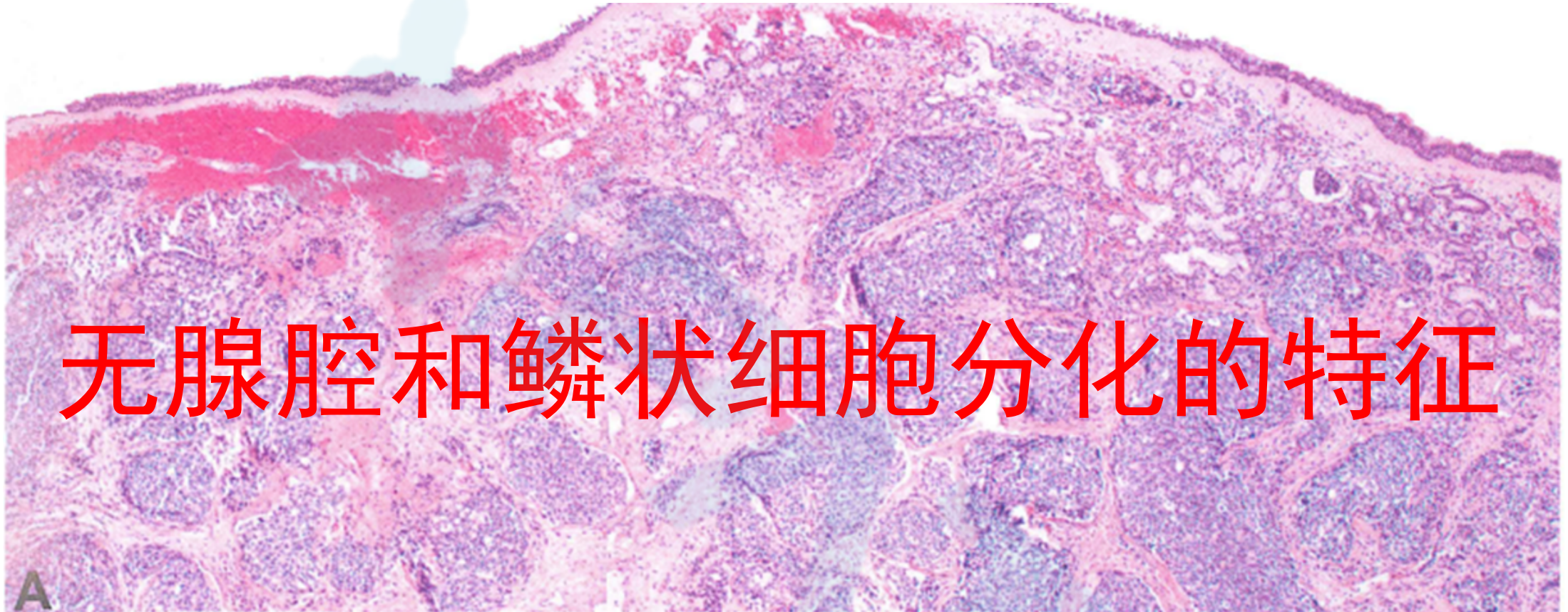
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鼻腔鼻窦未分化癌 (SNUC)

- 1986年首次报道
- is undifferentiated carcinomas of the sinonasal tract without glandular or squamous features and not otherwise classifiable.
- 罕见，占有所有鼻腔鼻窦癌的3-5%，发病率约0.02/100000。发病年龄范围广，青年到老年（平均年龄50-60岁）。
- 无明确发病因素，部分患者有吸烟史，如果有EBV或HPV感染，诊断SNUC需谨慎。
- 鼻腔和筛窦是常受累及的部位，肿瘤可单部位或多部位发病，肿瘤常常累及邻近结构，淋巴结转移少见。
- 鼻腔、鼻窦的症状（鼻塞、鼻出血、突眼、眶周肿胀、复视等），病程常较短。
- 大体 常大于4cm，霉菌样生长，边界不清，常破坏骨质和周围组织。

SNUC组织病理学

无腺腔和鳞状细胞分化的特征



SNUC免疫组化

- AE1/AE3+、CK7+、CK8+、CK18+、CK5/6-
- 鳞状上皮marks: P40-、P63可+、
- 神经内分泌marks: CgA灶+ 、syn灶+
- CEA-、S100-、CD45-、CR-

SNUC

遗传学

无特殊的遗传学基因改变

预后

预后差，中位生存期22.1个月，3年、5年、10年生存率44.3%、34.9%、31.3%。

- **NUT中线癌**
IHC-NUT单抗强表达
分子- NUT重排
- **SMARCB1 (INI1) 缺陷性鼻腔鼻窦癌**
IHC-SMARCB1 (INI1) 不表达
分子-SMARCB1突变

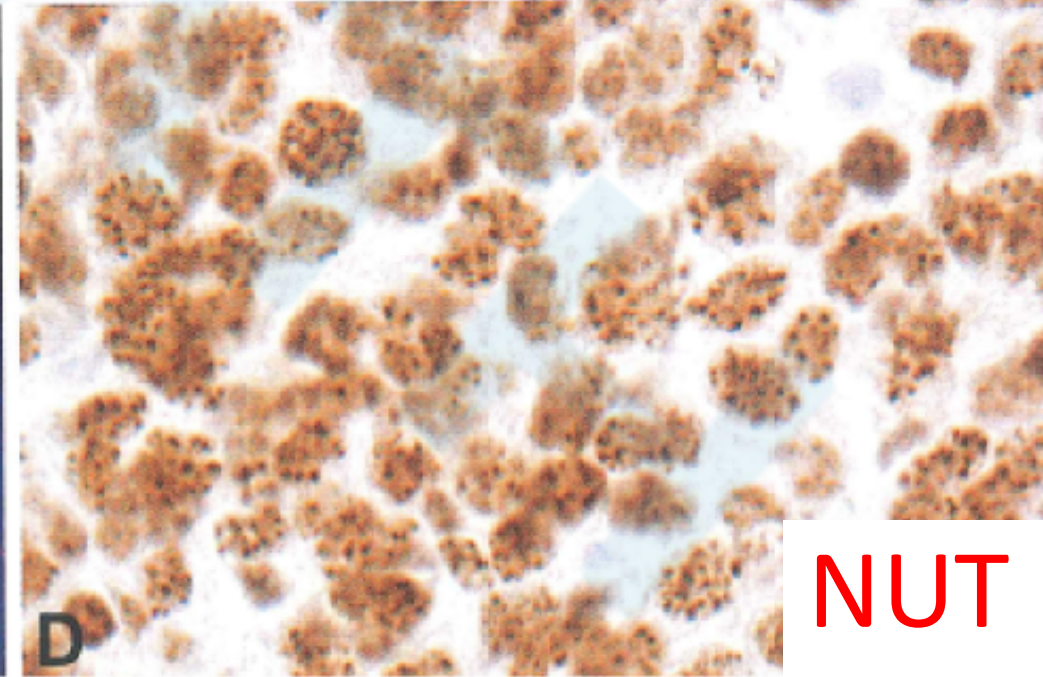
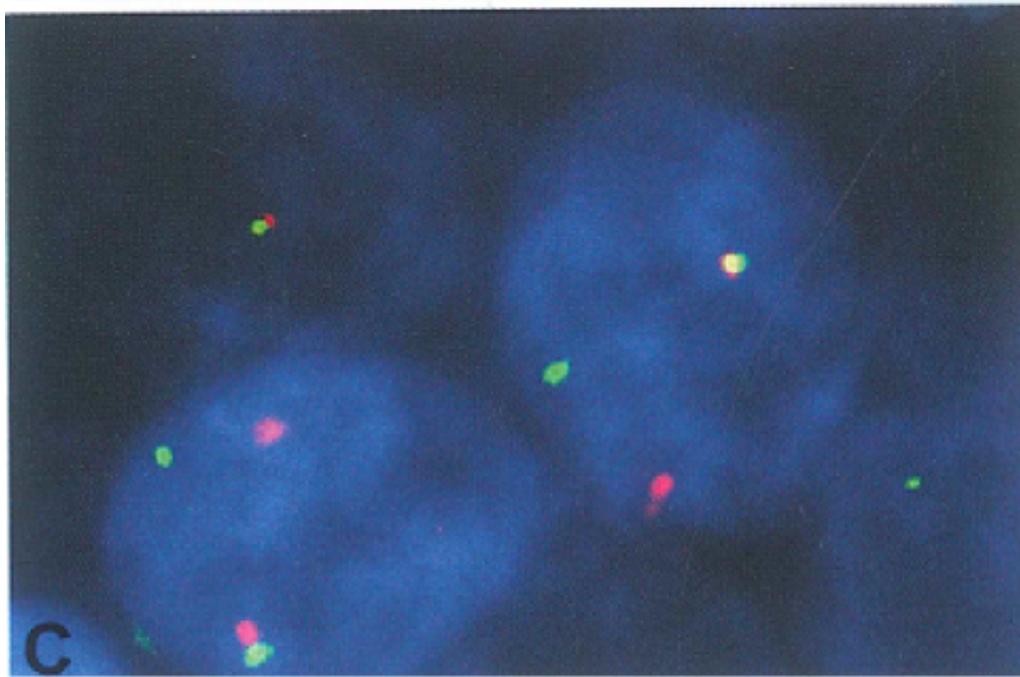
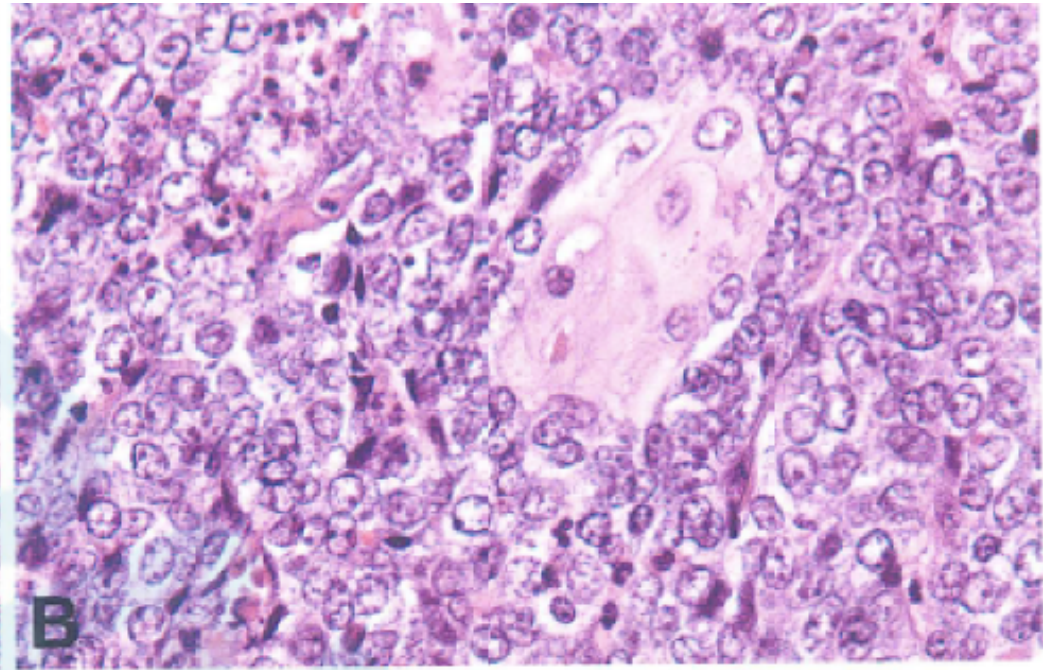
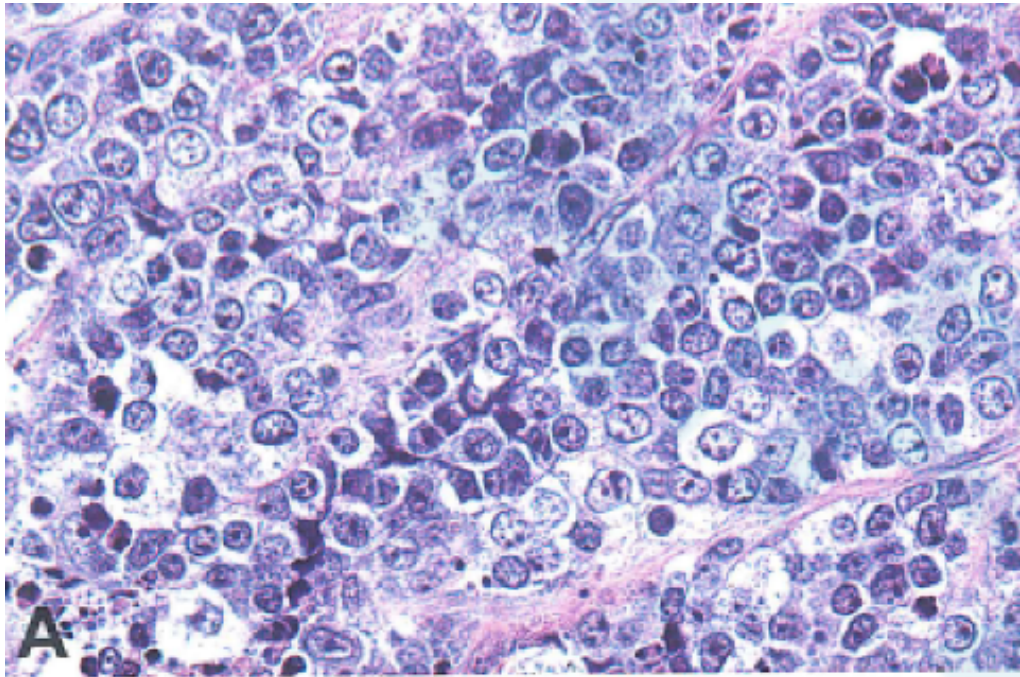
第四版头颈部WHO

Carcinomas

Keratinizing squamous cell carcinoma
 Non-keratinizing squamous cell carcinoma
 Spindle cell (sarcomatoid) squamous cell carcinoma
 Lymphoepithelial carcinoma
 Sinonasal undifferentiated carcinoma
 NUT carcinoma
 Neuroendocrine carcinoma
 Adenocarcinoma
 Intestinal-type adenocarcinoma
 Non-intestinal-type adenocarcinoma

try. Recently, a subset of undifferentiated carcinomas with rhabdoid features and a lack of SMARCB1 (INI1) protein by immunohistochemistry has been reported. It is unclear whether these tumours constitute a distinct entity [198].

NUT癌



NUT

SMARCB1 (INI1) 缺陷性SNUC

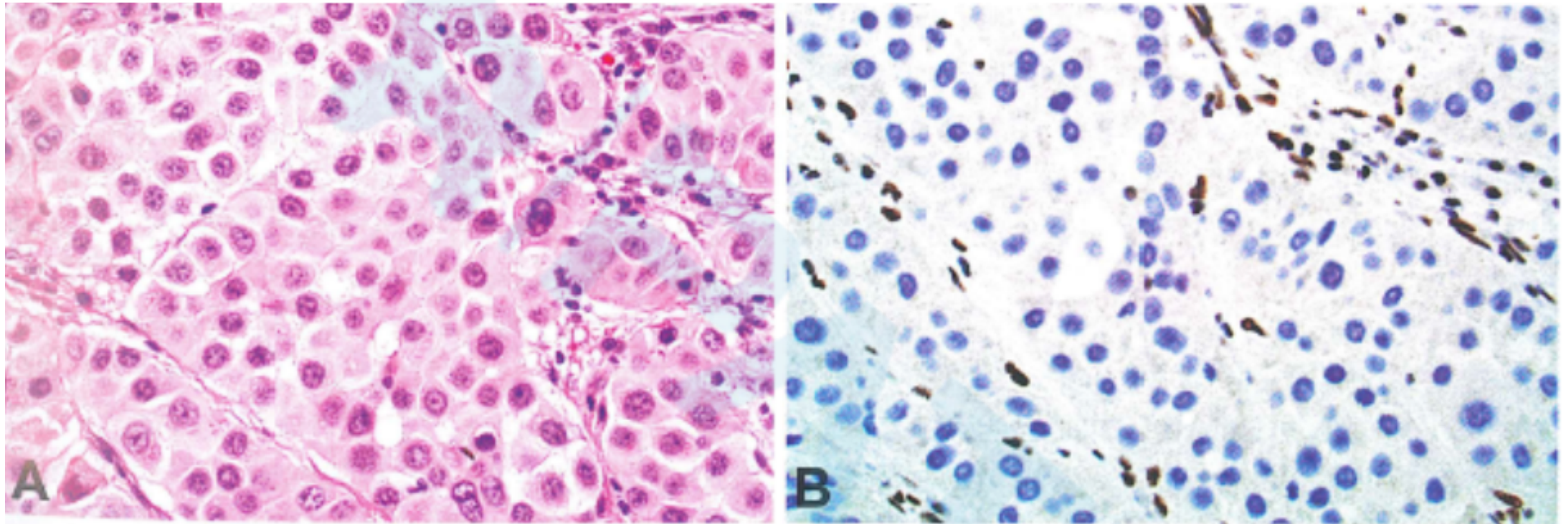


Fig. 1.08 SMARCB1-deficient sinonasal carcinoma. **A** Tumour composed of epithelioid nests of large, undifferentiated cells with abundant, eccentrically located eosinophilic cytoplasm and large round nuclei with prominent nucleoli, imparting a rhabdoid appearance. **B** Tumour is entirely negative for SMARCB1 by immunohistochemistry; associated benign lymphocytes and stromal cells serve as a useful positive control.

注：2017版头颈部WHO未将SMARCB1 (INI1) 缺陷性SNUC作为一种独立肿瘤类型

SMARCB1 (INI1)

- SMARCB1 (INI1) 位于22q, 是SWI/SNF染色质重塑复合物的核心亚基。调节基因表达和细胞分化过程。
- SMARCB1 (INI1) 基因失活是由于纯合子丢失, 失活突变等
- SMARCB1 (INI1) 等位基因失活, IHC -SMARCB1 (INI1) 核不表达。

SWI / SNF （酵母交配型转换 / 蔗糖不发酵复合物）

- 是20 世纪90 年代初在酿酒酵母中发现的一种ATP 依赖的染色质重塑复合物。
- 由>20个密切相关的蛋白组成，这些蛋白作为一个单位调节染色质重塑
- 核心亚基（包括SMARCB1）和两个催化亚基：SMARCA2（BRM）和SMARCA4（BRG1）
- 通过IHC方法检测SWI / SNF的亚基是否失活，使得SWI / SNF IHC成为识别和正确分类此类高侵袭性肿瘤的有价值的辅助工具。

SMARCA4 (BRG1)

- 位于19p13 ， 是一种磷酸化核蛋白
- 近些年研究认为SMARCA4失活是多种高侵袭性恶性肿瘤的主要驱动因素
- **SMARCA4缺陷性肿瘤：** 卵巢高钙血症型小细胞癌（90%）、源自胸腔和子宫的高侵袭性大细胞恶性肿瘤、非小细胞肺癌亚型、不同器官的去分化/未分化的癌。
- 只报道了2例SMARCA4缺陷性鼻腔鼻窦癌（本作者学组报道了一例， case1）。

本文通过IHC检测SMARCA4进一步研究SMARCA4
缺陷性鼻腔鼻窦未分化癌

MATERIALS AND METHODS

- IHC :AE1/AE3, CK7, p63, CK5,CgA , syn, CD56, NUT, SMARCB1 (INI1),SMARCA2 , SMARCA4 (BRG1)
 - 仅对活的肿瘤组织的细胞核进行评估（远离坏死区域）
背景中正常非肿瘤细胞核均匀强染色是评估染色成功与否的先决条件。
 - 回顾性研究组织样本： provided by the local ethics committee of the Friedrich-Alexander University Erlangen-Nuremberg (January 24, 2005 and January 18, 2012).
 - 分子检测
- case 4 DNA进行致病性突变检测（ST170 基因面板包括IDH1 和 IDH2）

RESULTS-Clinical Features

TABLE 1. Clinicopathologic Features of SMARCA4-deficient Sinonasal Carcinomas (n = 10)

No.	Age/Sex	Site	Original Diagnosis	Predominant Histology	Initial Stage	Treatment	Site/Time of MTS (mo)	Outcome/Follow-up (mo)
1	40/F	Right nasal cavity +sinuses	NEC	Basaloid small cells	T4N2M0	Surgery+RT	—	AWD (9)
2	50/M	Nasal cavity left	NEC vs. ONB	Basaloid small cells	NA	NA	NA	NA
3	20/M	Nasal cavity left	Large cell NEC	Large and rhabdoid cells	T4NXM1	Chemotherapy	Brain invasion	DOD (3 mo)
4	47/M	Sinonasal unspecified	Large cell NEC	Large cells	T4NxM1	Chemotherapy	Multiple vertebral, liver	AWD (8)
5	30/M	Nasal cavity	NEC	Large cells	NA	NA	NA	NA
6	41/M	Nasal cavity	Poorly differentiated malignancy	Large cells	NA	NA	NA	NA
7	51/F	Sinonasal unspecified	Small cell NEC	Basaloid small cells	NA	Surgery	NA	Died 3 mo after surgery before planned RT
8	42/F	Left nasal cavity and maxillary sinus	Poorly differentiated carcinoma	Large rhabdoid cells	T4NxM1	Chemotherapy	Lung/mediastinal metastasis at presentation	Died of progressive lung disease at 7 mo
9	67/M	Right nasal cavity	Poorly differentiated carcinoma	Large rhabdoid cells	T4NxMx	NA	NA	NA
10	54/M	Left nasal cavity	SNUC	Nested large cells	T4NxMx	Biopsy only	NA	DOD (1 mo)

AWD indicates alive with disease; DOD, died of disease; F, female; M, male; MTS, metastasis; NA, not available; ONB, olfactory neuroblastoma; RT, radiotherapy.

RESULTS-Clinical Features

- 7男3女
- 年龄：20-67岁（中位年龄44岁）。
- 部位：鼻腔（6）、鼻腔及鼻窦（2）、不清楚（2）
- 原始诊断：6例小细胞神经内分泌癌（SCNEC）或大细胞神经内分泌癌（LCNEC），3例低分化肿瘤/癌，1例SNUC
- 主要细胞学形态：基底细胞样小细胞（3）、大横纹肌样细胞（3）、大细胞（4）
- 肿瘤分期都是T4（6）；
 - 3例发生转移的患者仅接受了化疗（颈淋巴结+ 肺1例，肝脏+骨1例，肺+纵隔一例）；1例随访3个月死亡，一例随访8个月后带病生存，一例 随访7个月后死于肺部疾病进展
 - 2例患者接受手术（其中一例还接受辅助性治疗），1例随访9个月后带病生存，另一例于术后三个月辅助性治疗之前死亡。
 - 1例（case10）仅穿刺活检原始诊断SNUC，随访一个月死亡
 - 4/6（66%）随访中死于疾病（随访中位时间, 3 m），其他2个人姑息性治疗后带病生存。

RESULTS-Pathologic Findings

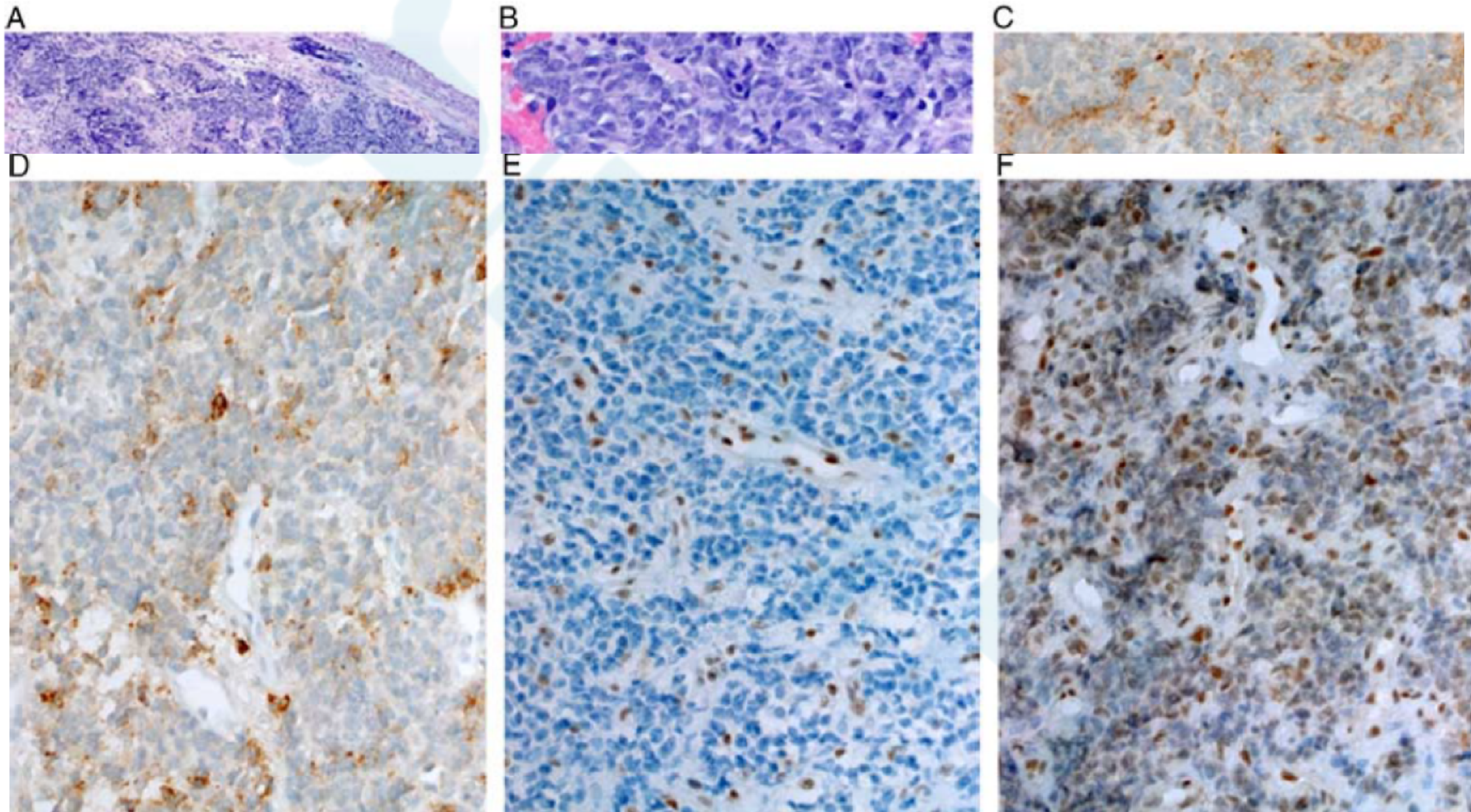


FIGURE 1. Three of SMARCA4-deficient sinonasal carcinomas showed small cell carcinoma-like pattern covered by surface epithelium which lacked dysplasia (A, B). Synaptophysin (C) and CD56 (D) as highly sensitive neuroendocrine markers showed only very limited and weak expression. Loss of SMARCA4 is a defining feature of all cases (E). F, SMARCA2 was very weak but still recognizable in the tumor cell nuclei (poor staining due to suboptimal tissue preservation).

RESULTS-Pathologic Findings

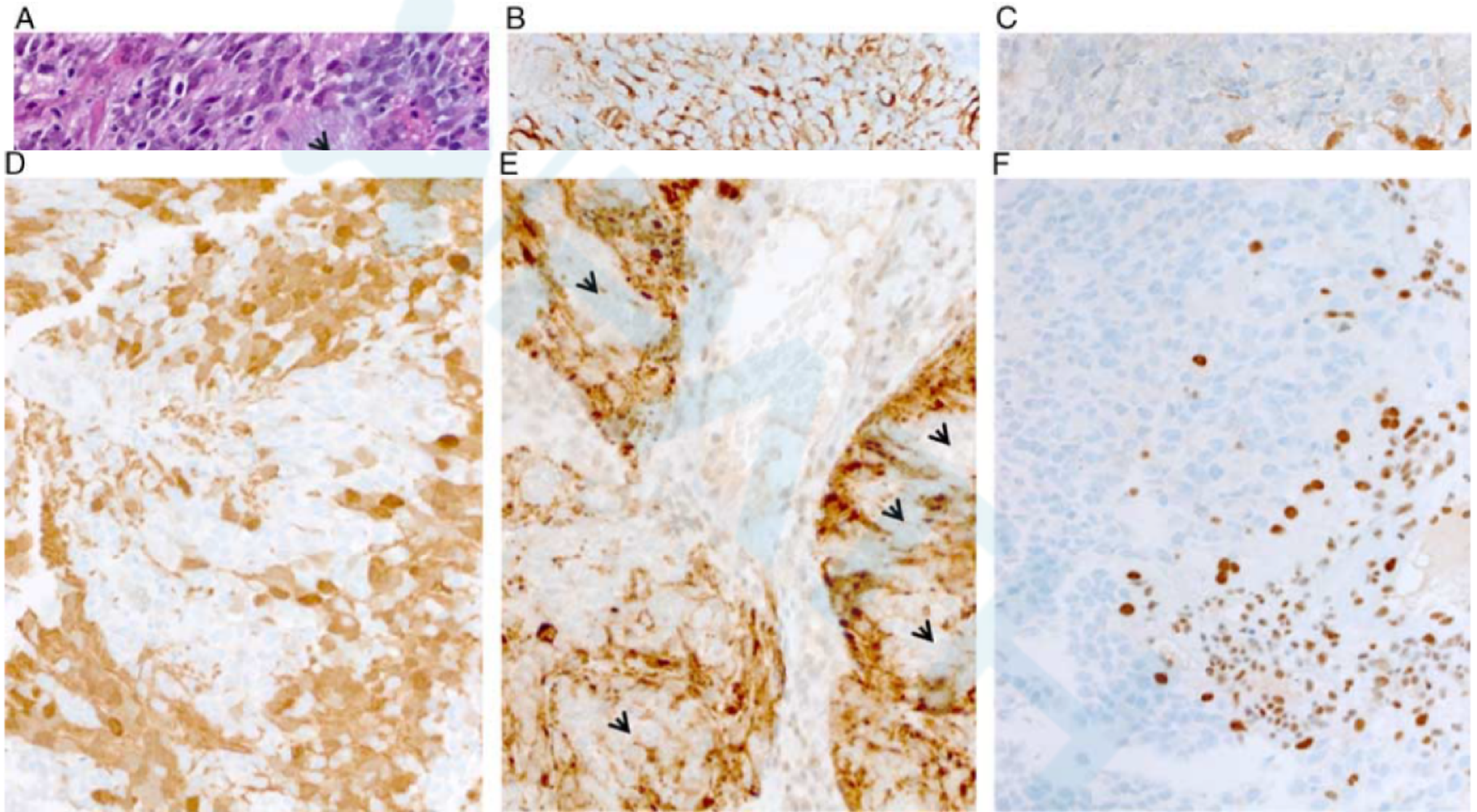


FIGURE 2. This unusual SMARCA4-deficient sinonasal carcinoma (A) showed small cell pattern admixed with neuroepithelial-like bland aggregates (arrows) and strongly expressed pankeratin (B). S100 was expressed in a sustentacular pattern (C). Same cell population expressed Calretinin (D) and synaptophysin (arrows highlight nonstaining neoplastic cells amid these neuroepithelial-like elements [E]). F, Complete loss of SMARCA4 limited to the small cell population (sustentacular-like cells and inflammatory cells are strongly positive).

RESULTS-Pathologic Findings

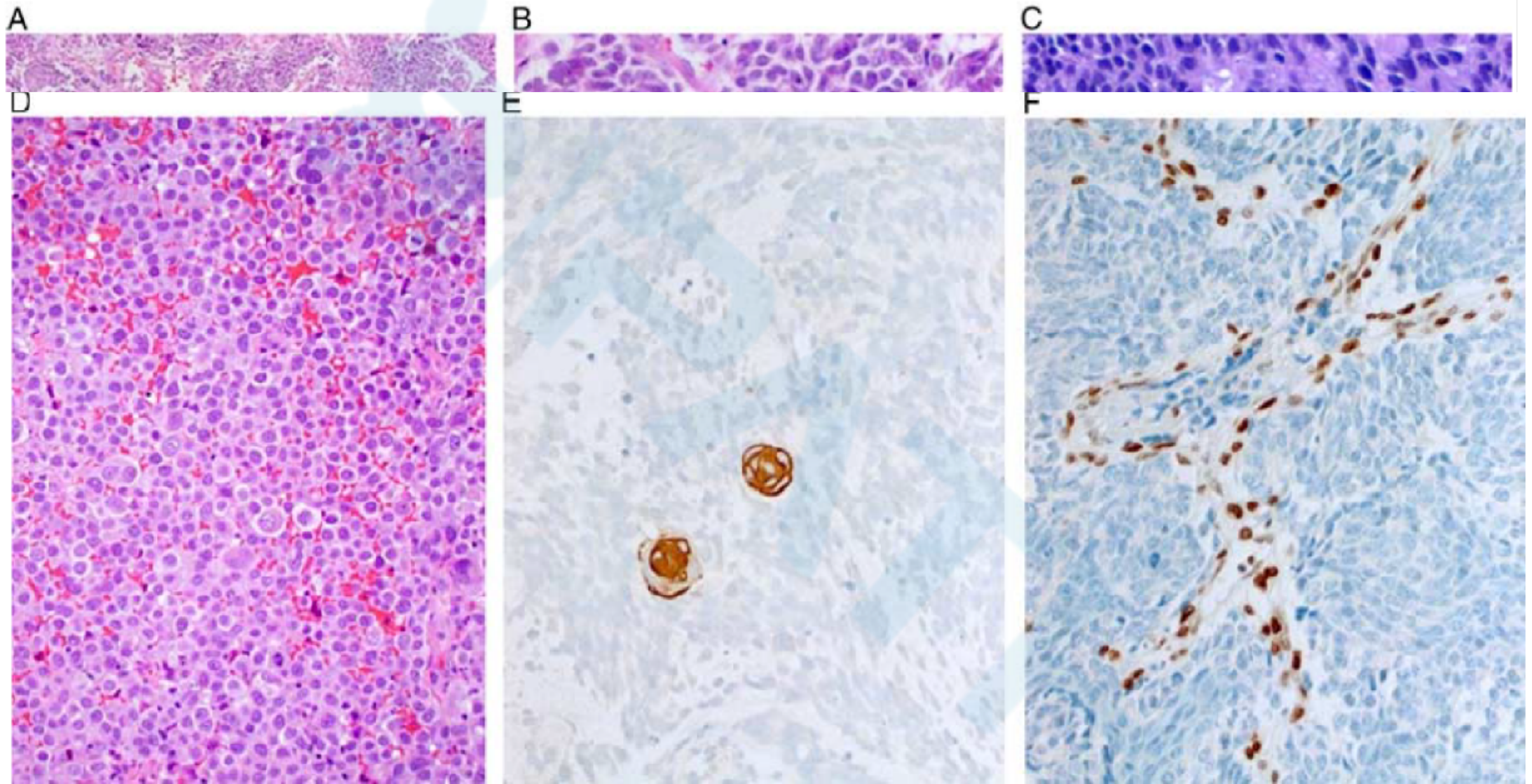


FIGURE 3. The large cell pattern of SMARCA4-deficient sinonasal carcinoma was closely similar to classical SNUC with prominent communicating nests and aggregates (A, B) occasionally with extensive stromal fibrotic reaction entrapping minute nests (A inset). C, One tumor showed focal abortive rosettes but lacked neuroendocrine differentiation by IHC. D, Another case showed admixture of poorly cohesive medium-sized and large rhabdoid cells. CK5 was negative in the neoplastic cells, highlighting a few reactive metaplastic squamous islands (E). F, Complete loss of SMARCA4 with strong retained expression in vascular endothelium highlighting the prominent nesting.

RESULTS- Immunohistochemical Findings

TABLE 2. Immunohistochemical Findings in SMARCA4-deficient Sinonasal Carcinomas (n = 10)

No.	Pan-CK	CK7	p63	CK5	CHgA	SYN	TTF1	CD56	p16	NUT	SMARCB1	SMARCA4	SMARCA2
1	Pos	Neg	Neg	Neg	Neg	+(wk)	Neg	+(wk)	ND	Neg	Retained	Loss	Reduced
2	Pos	Neg	Neg	Neg	F+	+++	Neg	+	Neg	Neg	Retained	Loss	Retained
3	Pos	Neg	Neg	Neg	Neg	Wk+	Neg	F+	ND	Neg	Retained	Loss	Loss
4	Pos	F+	Neg	Neg	Neg	++	Neg	Neg	ND	Neg	Retained	Loss	Retained
5	Pos	ND	Neg	Neg	F+	F+	Neg	ND	Neg	Neg	Retained	Loss	Retained
6	Pos	ND	Neg	Neg	F+	F+	Neg	ND	Neg	Neg	Retained	Loss	Retained
7	Pos	ND	Neg	Neg	F+	F+	Neg	ND	Neg	Neg	Retained	Loss	Reduced
8	Pos	Neg	Neg	Neg	Neg	Neg	Neg	ND	Neg	ND	Retained	Loss	Retained
9	Pos	ND	Neg	Neg	Neg	Wk+	ND	ND	ND	ND	Retained	Loss	ND
10	Pos	F+	Neg	Neg	Neg	i+	Neg	Neg	ND	Neg	Retained	Loss	ND

CHgA indicates chromogranin A; CK, cytokeratin; F, focal; ND, not done; Neg, negative; NR, no assessable results due to poor tissue preservation and/or staining quality; Pos, positive; SYN, synaptophysin.

1. pankeratin (10/10); CK5 、 P63 、 NUT 、 TTF1均不表达;
2. CK7 (2/6灶+) , syn (9/10灶+) , CgA (4/10灶弱+), CD56 (3/5灶+) ;
p16 (5/5-) , TTF1 (9/9-);
3. 所有肿瘤SMARCA4完全不表达(Figs. 1E, 2F, 3F), SMARCB1/INI1均表达,
(1/8) SMARCA2 和SMARCA4共缺失;
4. 基因检测: (case 4) 无基因突变

DISCUSSION

SNUC成为 “垃圾桶”

- 自1986年命名之后SNUC诊断使用太宽泛
- SNUC罕见，普通外科病理医生经验有限
- 没有可重复的免疫表型和/或遗传标记

近些年研究致力于低分化鼻腔鼻窦癌（ SNUC和SNUC样癌）
的分子分型

（先进分子技术、形态及免疫表型）

NUT癌和SMARCB1缺陷性癌

VS NUT癌

- 误诊为SNUC（纯未分化小细胞或大细胞形态）
- 误诊为低分化鳞状细胞癌（偶见鳞状细胞分化）
- 基底细胞样低分化肿瘤 伴鳞状细胞表型及神经内分泌或神经外胚层特征，检测到EWSR1 基因融合，归为鼻腔鼻窦尤文肉瘤的变异型（称之为造釉细胞瘤样变异型）。

DISCUSSION

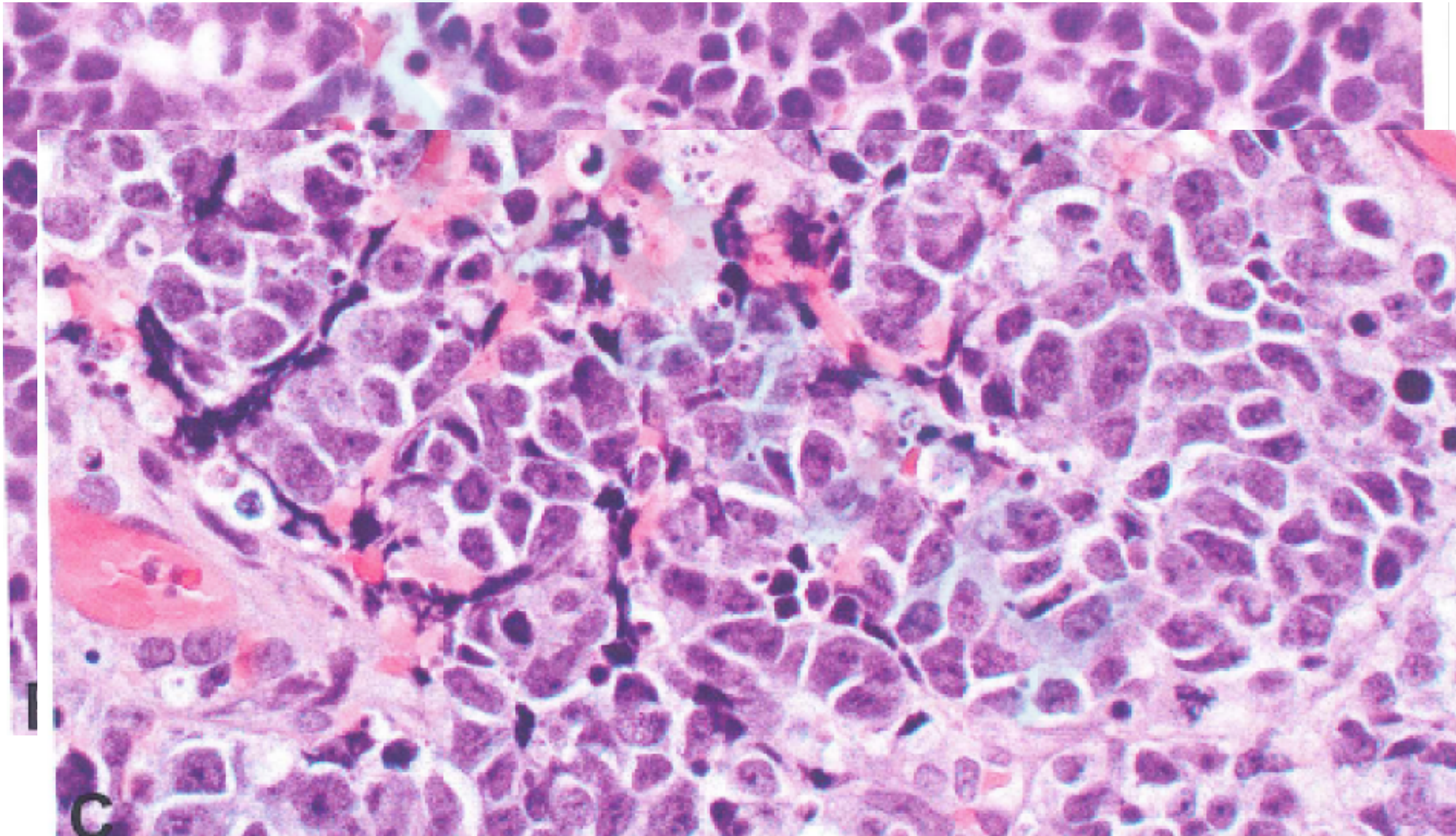
“SMARCB1 缺陷性鼻腔鼻窦腺癌”

- SMARCB1 恒定失活（唯一的潜在异常基因）。
- 主要是未分化的基底细胞样细胞伴少量的横纹肌样细胞，偶见嗜伊红 “粉红色” 嗜酸性胞浆和真正的腺腔结构。
- 大部分病例原始诊断为SNUC

VS Large and small cell NEC

- **问题和困惑** SNUC (伴或不伴SWI/SNF缺失)神经内分泌标记局灶或斑片状表达，且神经分泌分化的形态学证据不足，能诊断NEC? 不能
- **SWI/ SNF缺陷性肿瘤诊断NEC应该谨慎，只有HE细胞学和结构都是典型的神经内分泌肿瘤特征，且IHC也支持时方可诊断。**

SNUC鉴别诊断-神经内分泌癌



DISCUSSION

- SWI/SNF的不同亚基的功能是在一个高度协调的状态下实现的。因此，不同亚基的缺失会使肿瘤有类似的表型。
- 假定SWI/SNF作为致病性基因的不同亚基之间可以互相替代，比如SMARCA4在上皮样肉瘤和儿童恶性横纹肌样肿瘤中是失活的，但SMARCB1保留。一例非常类似SMARCB1缺陷性SNUC，IHC显示SMARCB1表达，而SMARCA4是缺失的。表明SMARCA4是作为同一复合物的替代基因发挥作用的。

DISCUSSION

经典的SNUC的分子发病机制研究-unknown

- Jo et al发现 IDH2 在55% SNUC突变，而 IDH2野生型病例中有一例SMARCA4 失活突变，且IHC已证实SMARCA4蛋白丢失。
- 有研究显示形态学定义的SNUC中， IDH2 R172X 突变率高达82%，而5例SMARCB1缺陷性SNUC无 IDH2 突变。
- SNUC中SMARCB1/CA4失活与 IDH2 突变互相排斥

DISCUSSION

- 本文：CASE4 分子检测且无IDH2 突变，因此，SMARCA4缺陷性SNUC不可能隐藏IDH2突变。
- SMARCB1缺陷性SNUC中除了SMARCB1失活之外，无额外的分子改变
- 综上，SMARCA4缺陷性SNUC能作为不同于IDH2突变的SNUC的一个独立的肿瘤实体吗？
- 还需要进一步研究

CONCLUSION

1. 本文描述了10例一类特殊的鼻腔鼻窦未分化癌，
细胞以未分化的大细胞形态为主，小细胞形态次之，
始终缺乏任何特定的分化方向，同时
SMARCA4基因失活及蛋白表达丢失。
2. 这种临床上高侵袭性肿瘤实体增加了SWI/ SNF驱
使的低分化鼻腔鼻窦癌的疾病谱。

SMARCA4缺陷性SNUC	SMARCB1缺陷性SNUC	经典SNUC
临床特点及人口统计学相似		
单一形态的未分化大上皮样细胞排列无特征性，核仁显著		
大细胞为主，小细胞次之，（小细胞癌样）	大的上皮样细胞，胞浆丰富、嗜酸	肿瘤细胞呈显著的大巢状排列
神经内分泌标志物常表达（不恒定且染色较弱）； 鳞状上皮markers不表达	鳞状细胞markers可表达(64%CK5+，55%p63 +)	神经内分泌标志物常表达（不恒定且染色较弱）；
SMARCA4失活	SMARCB1失活	Unknown，55%IDH2突变

Thanks