

• 病例报告 •

1例鼻窦SMARCA4缺失性癌伴颅内侵袭临床病理学分析

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[关键词] SWI/SNF 复合体; 鼻窦 SMARCA4 缺失性癌; 鉴别诊断

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Clinicopathological analysis of a case of sinonasal SMARCA4-deficient carcinoma with intracranial invasion

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[Key words] SWI/SNF complex; sinonasal SMARCA4-deficient carcinoma; differential diagnosis

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鼻窦 SWI/SNF 相关 BAF 染色质重塑复合物亚基 ATP 酶 4 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4, SMARCA4) 缺失性癌是 2022 年世界卫生组织 (World Health Organization, WHO) 头颈肿瘤分类第 5 版中的新增类型, 作为鼻窦 SWI/SNF 复合体缺失性癌的一个亚型, 其约占低/未分化鼻窦癌的 4%^[1]。该肿瘤较为罕见, 文献报道少且缺乏特异性的分化特征, 临床上易被误诊为其他类型的恶性肿瘤。本文将探讨 1 例伴颅内侵袭的鼻窦 SMARCA4 缺失性癌, 分析其临床病理特征及分子特点, 并回顾相关文献, 旨在提高对这一特殊肿瘤类型的认知, 为临床诊断、治疗及预后评估提供关键信息。

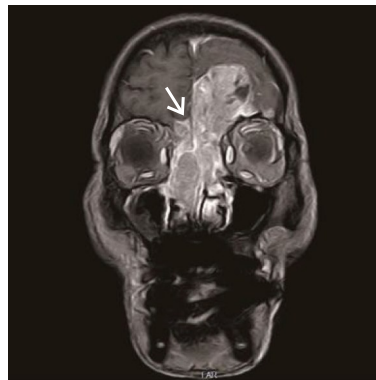
1 病例资料

患者男, 70 岁, 因“记忆力进行性下降 3 d”入院, MRI 提示鼻腔、双侧筛窦及左侧额叶片状异常信

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号, T1WI 低信号, T2WI 稍高信号, DWI 呈高信号, 信号不均, 大小约 6.5 cm×6.5 cm, 增强扫描见明显不均匀强化 (图 1)。根据其连续性及其脑实质受压情况, 考虑颅内占位来自鼻腔。计划一期手术切除颅内肿瘤, 待颅内病情稳定后行二期手术切除鼻腔内占位性病变。术中见肿瘤呈红黑色, 质韧, 血供极其丰富, 侵犯嗅神经。



MRI contrast-enhanced scan shows a large space-occupying lesion in the nasal cavity, bilateral ethmoid sinuses, and left frontal lobe (arrow).

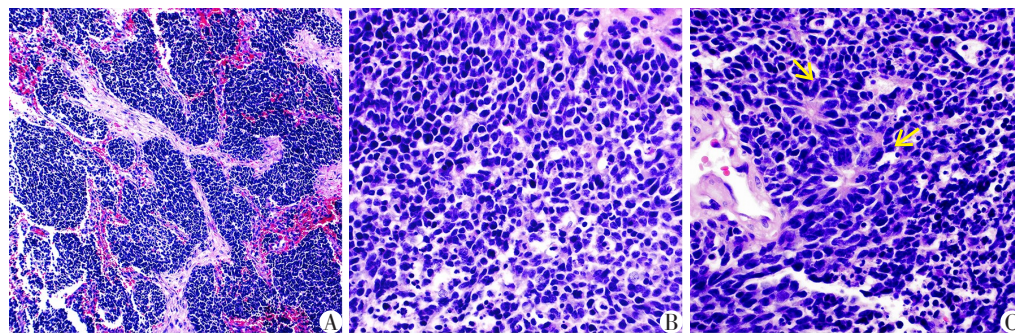
图 1 患者 MRI 增强扫描

Figure 1 MRI contrast-enhanced scan of the patient

标本经 10%中性甲醛固定,常规脱水,石蜡包埋,4 μm 厚切片,行 HE、免疫组化 EnVision 法染色,通过 Roche Benchmark GS 全自动免疫组化机进行。大体见灰白灰红色碎组织一堆,大小合计 6 cm \times 6 cm \times 1 cm,切面灰红色,质嫩。低倍镜下肿瘤呈浸润性生长,侵犯脑组织。肿瘤细胞呈弥漫实性、片状或巢团状分布(图 2A),伴广泛出血、坏死;间质显著纤维化,富于血管。高倍镜下,肿瘤细胞卵圆形或多边形,中等大小,呈基底样细胞特征,核浆比高,核深染,核仁不明显,核分裂象易见,可见病理性核分裂象(图 2B),小灶出现菊形团样结构(图 2C)。肿瘤细胞表达上皮标记 AE1/AE3、EMA 及 CAM5.2,神经内分泌标记 CgA、Syn(图 3A)、INSM1 部分阳性,SMARCA4/BRG1 表达缺失(内对照血管内皮及间质细胞阳性)(图 3B),SMARCB1/INI-1 保留表达(图 3C),Ki-67 增殖指数 70%(图 3D),P40 少量表达,余 Desmin、MyoD1、NKX2.2、GFAP、S-100、HMB-45、TTF-1 及 EB 病毒原位杂交 EBER 均阴性。

下一代测序(next-generation sequencing, NGS)检测从石蜡包埋组织样本中提取 DNA,采用南京世和基因生物技术有限公司 DNA 测序产品,测序平台为 Illumina 高通量测序平台。检测结果显示 SMARCA4 第 8 外显子 c.1252C>T(p.Q418*) 无义突变(图 4A),CTNNB1 第 3 外显子 c.134C>T(p.S45F) 错义突变(图 4B)。

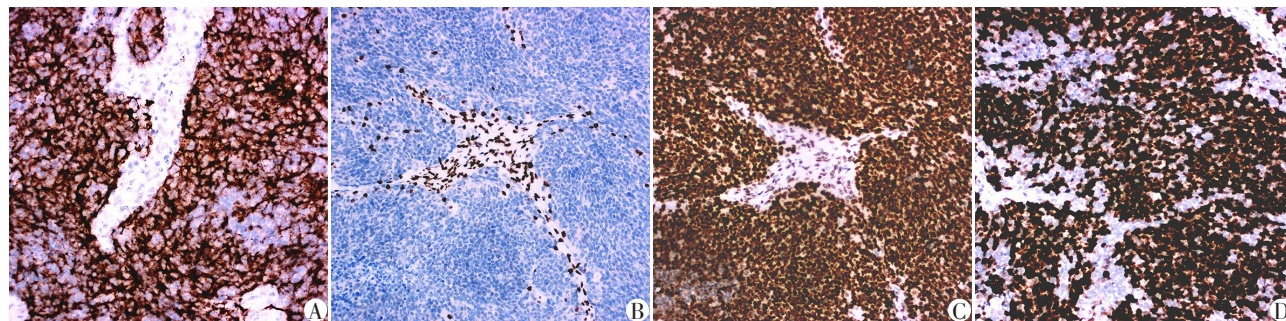
利用 cBioPortal 数据库(<https://www.cbioportal.org>)查询头颈部肿瘤及泛癌中 SMARCA4 与 CTNNB1 的突变情况,并分析其生存预后。生物信息分析结果显示 SMARCA4 与 CTNNB1 突变在头颈部肿瘤中的共现率较低(164 例 SMARCA4 突变,62 例 CTNNB1 突变,仅 10 例共突变),样本量不足导致难以进行有统计学意义的解读。然而,在泛癌种数据分析中获得了更具规模的队列:3 579 例 SMARCA4 突变,2 815 例 CTNNB1 突变,308 例共突变,对应 8.6% 的共突变率。值得注意的是,生存分析显示共突变组与仅 SMARCA4 突变组的预后差异有统计学意义



A: The tumor exhibits solid nest-like distribution($\times 100$). B: Tumor cells exhibit morphological heterogeneity, characterized by their oval or polygonal shape, medium size, basaloid cell characteristics, and a high nuclear-to-cytoplasmic ratio. The nuclei are hyperchromatic with dense chromatin, and nucleoli are inconspicuous. Mitotic figures are readily observed, indicating active cell division($\times 400$). C: Focal rosette-like structures are observed (arrow)($\times 400$).

图2 鼻窦SMARCA4 缺失性癌组织学形态(HE 染色)

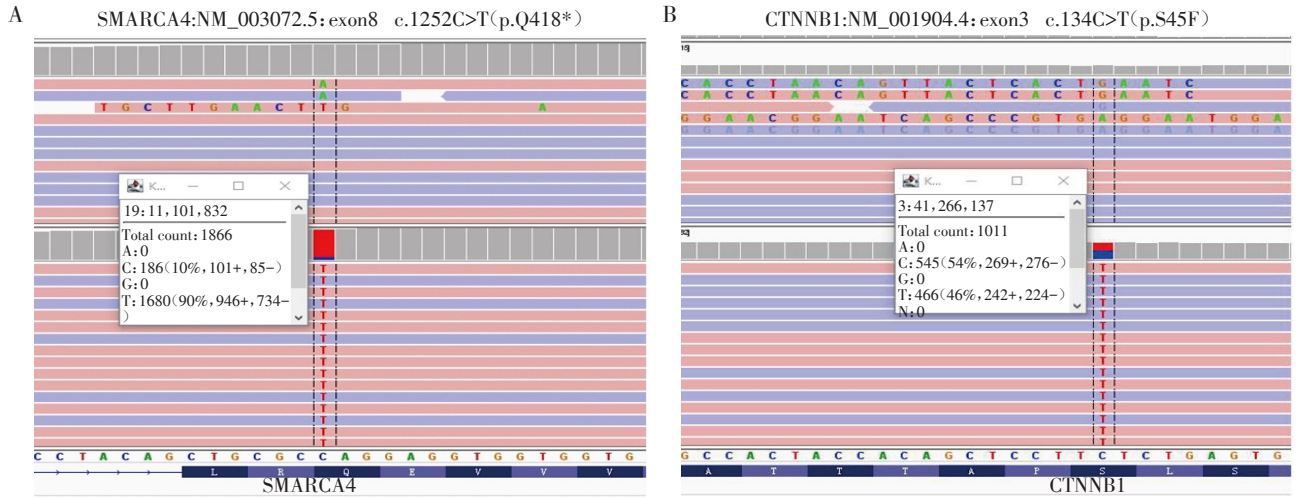
Figure 2 Histological morphology of sinonasal SMARCA4-deficient carcinoma(HE staining)



A: Syn is positive in tumor tissue. B: Tumor cells show complete loss of SMARCA4/BRG1 expression, with positive internal control stromal fibroblasts. C: Tumor cells retain SMARCB1/INI-1 expression. D: Tumor cells exhibit a high Ki-67 proliferation index($\times 200$).

图3 鼻窦SMARCA4 缺失性癌免疫表型

Figure 3 Immunophenotype of sinonasal SMARCA4-deficient carcinoma



A: SMARCA4 exon 8 c.1252C>T(p.Q418*) nonsense mutation were detected by NGS method. B: CTNNB1 exon 3 c.134C>T(p.S45F) missense mutation were detected by NGS method.

图4 NGS检测结果

Figure 4 NGS results

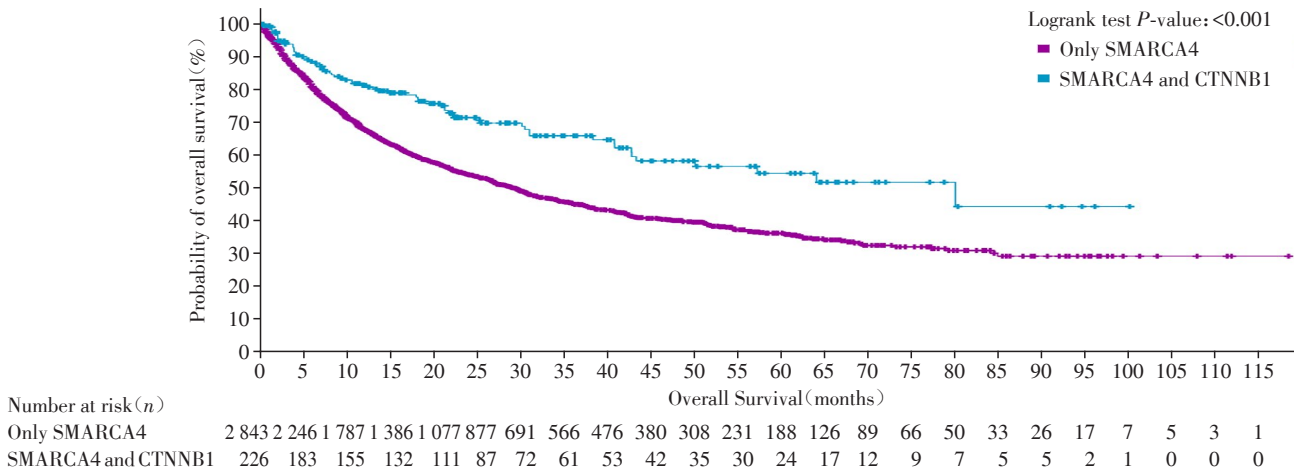
($P < 0.001$), 共突变患者预后明显更差(图5)。

患者于术后2个月出现言语障碍,复查头颅CT显示双侧鼻腔、副鼻窦腔及额叶不规则软组织密度灶,伴邻近骨质破坏,部分病灶内出血,病变范围较术前扩大。患者术后恢复状况不佳,于术后3个月不幸去世。

2 讨论

根据遗传学和形态学的差异,鼻窦SWI/SNF缺失性癌包括SMARCB1缺失性癌、SMARCB1缺失性腺癌和SMARCA4缺失性癌。鼻窦SMARCA4缺失性癌最早于2017年报道^[2],到目前为止全球报道约

30例^[3-9](表1)。鼻窦SMARCA4缺失性癌的发病年龄20~83岁,男性多见。组织学上,肿瘤由小的基底样细胞或大的上皮样细胞组成,形成巢状和实性片状结构,伴有广泛的坏死。免疫组织化学显示肿瘤均表达广谱上皮标记AE1/AE3,不表达鳞状上皮标志物CK5/6、p63及p16、NUT。其他标志物如CK7、Syn、CgA和CD56的表达不一。所有肿瘤均显示SMARCA4/BRG1完全缺失,而SMARCB1/INI1表达保留。个别病例显示SMARCA2的共缺失^[9]。本例患者肿瘤达6.5 cm×6.5 cm,伴广泛颅内侵袭,为目前文献中最大且侵袭范围最广的病例。影像学显示肿瘤自鼻腔经筛板侵入左侧额叶,MRI中DWI高



Pan-cancer survival analysis revealed that the difference in outcomes between the SMARCA4/CTNNB1 co-mutation group and the SMARCA4-only mutation group was statistically significant ($P < 0.001$).

图5 生物信息分析结果

Figure 5 Results of bioinformatics analysis

表1 鼻窦SMARCA4缺失性癌的临床特征文献报道汇总表

Summary Table of Literature Reports on Clinical Characteristics of Sinonasal SMARCA4-Deficient Carcinoma

References	Age/sex	Site	Size (cm)	TNM/metastasis	Treatment	Survival(month)	SMARCA2 expression
AGAIMY A ^[2]	40/F	right nasal cavity, sinuses; skull base and periorbital extension	NA	T4N2M0	Surgery+RT+CT	AWD(9)	Reduced
	40/F	right nasal cavity, sinuses	NA	T4N2M0	Surgery+RT	AWD(9)	Reduced
	50/M	left nasal cavity	NA	NA	NA	NA	Retained
	20/M	left nasal cavity	NA	T4NXM1	CT	DOD(3)	Loss
	47/M	sinonasal unspecified	NA	T4NxM1	CT	AWD(8)	Retained
	30/M	nasal cavity	NA	NA	NA	NA	Retained
AGAIMY A ^[9]	41/M	nasal cavity	NA	NA	NA	NA	Retained
	51/F	sinonasal unspecified	NA	NA	Surgery	Died 3 mo after surgery before planned RT	Retained
	42/F	left nasal cavity and maxillary sinus	NA	T4NxM1	CT	Died of progressive lung disease at 7 mo	Retained
	67/M	right nasal cavity	NA	T4NxMx	NA	NA	ND
KAKKAR A ^[1]	54/M	left nasal cavity	NA	T4NxMx	Biopsy only	DOD(1)	ND
	48/M	bilateral nasal cavities, sphenoid, ethmoid mass with intracranial extension	NA	NA	Surgery+RT+CT	AWD(35)	Retained
	70/M	right nasal cavity	NA	NA	CT	DOD(9)	Retained
	30/M	left nasal cavity; intracranial extension	NA	NA	CT	AWD(34)	Retained
	43/M	sinonasal mass, unspecified, with intracranial extension	NA	NA	Surgery+RT+CT	DOD(34)	Retained
	30/M	nasal cavity	NA	NA	Surgery+CT	DOD(14)	Retained
	25/M	left nasal cavity	NA	NA	Surgery	NA	Retained
	45/F	right nasal mass	NA	NA	Surgery	NA	Retained
	28/M	left nasal cavity mass, intracranial extension	NA	NA	Surgery	AWD(7)	Retained
	22/M	left sinonasal mass with intracranial extension	NA	NA	Biopsy only	AWD	ND
LI C ^[7]	31/M	left nasal cavity	3.3	NA	Surgery+RT+CT	AWD(5)	ND
ZHAO M ^[3]	83/M	right nasal cavity, ethmoid sinus; maxillary sinus, skullbase and periorbital tissue	4.4	T4N0M0	Surgery+RT+CT	DOD(12)	Retained
	61/F	left nasal cavity, ethmoid sinus; left frontal sinus, maxillary sinus and the skull base	4.6	T4N0M0	Surgery+RT+CT	DOD(4)	Retained
KANG H G ^[4]	47/F	nasalcavity	NA	T4bNxM0	Surgery+CT	AWD(10.4)	ND
	50/M	nasalcavity	NA	TxN2bM0	Surgery+RT	AWD(5.6)	ND
	34/M	left nasal cavity, maxillary sinus, orbit; intracranium	NA	NA	RT+CT	DOD(6)	ND
ZHU H J ^[6]	64/M	slope at the base of the middle cranial fossa	NA	NA	Surgery+CT	AWD(6)	ND
KE Q L ^[8]	60/M	right nasal cavity, ethmoidal sinus	4	NA	Surgery+RT+CT	AWD	ND
XU X N ^[5]	65/M	nasal cavity, ethmoid, sphenoid, skull-base, brain	NA	T4N0M0	Surgery+CT	DOD	ND
Our case	70/M	nasal cavity, bilateral ethmoid sinuses and left frontal lobe	6.5	T4NxMx	Surgery	DOD(3)	ND

NA, not available; CT, Chemotherapy; RT, radiotherapy; AWD, alive with disease; DOD, died of disease; ND, not done.

信号提示肿瘤细胞密度高、增殖活跃,与肿瘤Ki-67指数高及核分裂活跃的特征一致。肿瘤细胞异型性显著,并伴有Syn、CgA、INSM1等神经内分泌标志物的表达,极易误诊为神经内分泌癌,但SMARCA4的表达缺失和SMARCB1表达保留证实了SMARCA4缺失性癌的诊断。

鼻窦SMARCA4缺失性癌的组织形态缺乏特异性,在免疫组化初筛时往往仅表现为上皮和神经内分泌标志物的表达,容易导致误诊。为此,需与以下高侵袭性肿瘤进行鉴别:①鼻窦SMARCB1/INI1缺失性癌:主要以一致的基底样细胞为主,或以浆细胞样细胞/横纹肌样细胞为主,偶尔呈现梭形细胞形态。然而,免疫组化显示肿瘤细胞SMARCB1/INI1缺失,而保留SMARCA4/BRG1表达,这有助于与SMARCA4缺失性癌的鉴别。相比鼻窦SMARCB1缺失性癌,SMARCA4缺失性癌的病死率可能更高,且中位年龄更低^[9-10]。②NUT癌:更常见于年轻人和儿童,由单一未分化的基底样肿瘤细胞呈片状或巢状分布,核浆比高,核仁明显,常伴有坏死,部分病例表现为突然的鳞状分化。免疫组化通常显示鳞状表型,具有广谱上皮、p63、p40的表达。③横纹肌肉瘤:常见于头颈部,由不同分化阶段的横纹肌母细胞构成,细胞形态多样,呈圆形或梭形,排列方式可为束状、腺泡状或弥漫片状。免疫组化检测显示Desmin、MyoD1、myogenin的表达,但部分横纹肌肉瘤也会表达上皮标志物及神经内分泌标志物,尤其是Syn和CD56,易误诊为神经内分泌癌。④大细胞神经内分泌癌:常呈现器官样结构,并伴有坏死,肿瘤细胞体积较大,胞质丰富,染色质粗糙,核仁显著。其神经内分泌标志物的表达较其他肿瘤更为强烈且弥漫,常见P53和Rb突变。在Agaimy等^[9]报道的10例鼻窦SMARCA4缺失性癌中,有6例最初被误诊为小细胞神经内分泌癌或大细胞神经内分泌癌。SMARCA4缺失性癌的神经内分泌标志物表达通常为局灶弱阳性,结合SMARCA4表达缺失可明确鉴别。头颈部的多种上皮性恶性肿瘤、横纹肌肉瘤与大细胞神经内分泌癌在组织学形态上高度相似,部分神经内分泌标志物的表达存在一定非特异性,尤其在活检组织局限时更易误诊。深入了解相关肿瘤的组织学谱系、免疫组化特征及分子遗传学变化,并系统地进行鉴别,对最终明确诊断至关重要。

SMARCA4基因编码的蛋白BRG1是SWI/SNF染色质重塑复合体的核心ATP酶亚基,在调控基因转录中发挥关键作用。BRG1的功能缺失是SWI/

SNF缺陷型鼻窦癌的重要分子特征,其突变率较高,且与多种癌症的不良预后相关,包括相当比例的非小细胞肺癌和高钙血症型卵巢小细胞癌。SWI/SNF复合体通过调控染色质拓扑结构和基因表达,在维持基因组稳定性、调节细胞分化及抑制肿瘤发生中发挥核心作用^[11-12]。本病例中,SMARCA4第8外显子发生c.1252C>T(p.Q418*)无义突变,导致蛋白翻译提前终止,BRG1蛋白完全缺失(免疫组化阴性),提示SWI/SNF复合体功能失活。此外,这种特异性突变与预后不良有关,因为类似的SMARCA4改变与非小细胞肺癌和其他恶性肿瘤的生存率降低有关。SMARCA4缺失通过以下机制驱动肿瘤恶性表型^[13-15]:①染色质重塑失调:SMARCA4缺失导致关键基因(如CDKN2A、TP53)的异常沉默或激活,引发细胞周期紊乱与基因组不稳定性;②上皮-间质转化(epithelial-mesenchymal transition, EMT)激活:染色质可及性改变可能上调EMT相关转录因子(如SNAIL、ZEB1),增强肿瘤侵袭性;③化疗耐药性:SMARCA4缺失通过抑制IP3R3介导的线粒体钙信号通路,削弱化疗诱导的凋亡效应。值得注意的是,本病例同时检测到CTNNB1第3外显子c.134C>T(p.S45F)错义突变,该突变可能通过抑制 β -catenin磷酸化降解,导致 β -catenin异常稳定并持续激活Wnt/ β -catenin信号通路^[16-18]。SMARCA4失活与CTNNB1突变共存现象在鼻窦SMARCA4缺失性癌中偶见报道^[3],两者可能具有协同致癌效应^[19]。动物实验表明,SMARCA4缺失与CTNNB1激活可共同促进小脑髓母细胞瘤的发生^[20],其分子机制包括:① β -catenin/SMARCA4互作:突变型 β -catenin核聚集后直接结合SMARCA4蛋白,增强Wnt靶基因(如AXIN2、LEF1)转录^[21-22];②染色质结构异常:SWI/SNF复合体缺失导致染色质开放区域增加,使Wnt通路靶基因(如MYC、CCND1)更易被异常激活^[23]。泛癌生存分析表明,SMARCA4/CTNNB1共突变组的预后明显差于仅SMARCA4突变组。这种预后差异可能源于SMARCA4失活与CTNNB1突变协同作用形成的双重打击机制,该机制会促进肿瘤向更具侵袭性的表型发展。其临床表现为疾病进展迅速、预后极差,这正是SWI/SNF复合物缺陷型肿瘤的典型特征。

鼻窦SMARCA4缺失性癌具有高度侵袭性,仅次于NUT癌,是所有鼻窦癌中预后最差的类型之一^[24]。大多数患者在诊断时已处于晚期,有2/3的患者在1年内因病去世,中位生存时间3个月^[1,9]。本例临床病

程呈快速进展模式,突显了鼻窦SMARCA4缺失性癌的侵袭性生物学行为。患者于术后3个月死亡,与文献报道的中位生存期相符,提示肿瘤体积大和颅内侵袭可能是预后不良的独立危险因素。目前多采用手术治疗联合辅助放化疗,尚无针对鼻窦SMARCA4缺失性癌的获批药物,除既往报道SMARCA4缺失性肿瘤对基于铂类的化疗方案敏感外^[25],靶向EZH₂、CDK4/6以及组蛋白去乙酰化酶抑制剂、组蛋白甲基转移酶抑制剂和DNA甲基转移酶抑制剂的临床试验也显示出一定的治疗效果^[15,26-28]。此外,越来越多的证据表明,至少有一部分SWI/SNF缺失恶性肿瘤可能对免疫检查点抑制剂有良好的治疗反应^[27,29-30]。本例中,CTNNB1突变可能还代表了使用Wnt/ β -catenin通路的小分子抑制剂治疗这些高度侵袭性肿瘤的诱人前景。该类药物已被证明能够抑制移植瘤甚至原发瘤在小鼠模型中的生长,相关药物的临床试验正在进行中,其中包括PORCN抑制剂(如LGK974)、Tankyrase抑制剂(如XAV939)等^[31-33]。这些都支持对罕见恶性肿瘤进行精确分类,以探索和优化针对其特定的形态学和分子特征的治疗策略。

在鼻窦SMARCA4缺失性癌的临床实践中,早期诊断的优化至关重要。高侵袭性鼻腔鼻窦肿瘤进行SMARCA4/BRG1和SMARCB1/INI-1的免疫组化常规检测,对该类肿瘤的早期发现和治疗具有重要意义。结合NGS技术来筛查SMARCA4和CTNNB1的突变情况,可为患者提供更为精准的诊断信息,有助于提高治疗的针对性和有效性,从而改善患者预后。在治疗上采用手术联合辅助放化疗能够一定程度改善患者的预后。同时还应积极探索EZH₂抑制剂、CDK4/6抑制剂及免疫治疗等联合用药策略,以期进一步提高治疗效果。此外,验证Wnt通路抑制剂(例如LGK974)与表观遗传药物的协同效应,将为开发新的治疗策略提供科学依据,为未来的临床治疗提供新的思路和方法。

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李云、孙阳阳负责实验数据收集及论文初稿撰写。王更芳负责NGS检测及数据分析,并构建分子图谱可视化结果。周晓莉负责设计研究思路,撰写、编辑和审阅论文。

Author's Contributions:

LI Yun and SUN Yangyang were responsible for collecting

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