มะเร็งโพรงจมูกชนิด SMARCA4-deficient Sinonasal Carcinoma: รายงานผู้ป่วย 1 ราย และการทบทวนวรรณกรรม

ธีรสิทธ ไวยนันท์ พ.บ.
กลุ่มงานพยาธิวิทยากายวิภาค โรงพยาบาลราชวิถี ถนนพญาไท แขวงทุ่งพญาไท เขตราชเทวี กรุงเทพมหานคร 10400

SMARCA4-deficient Sinonasal Carcinoma: A Case Report and Literature Review

Teerasit Viyanant, M.D.
Department of Pathology, Rajavithi Hospital, Ratchawithi Road, Thung Phaya Thai, Ratchathewi, Bangkok, 10400, Thailand
Corresponding Author: Teerasit Viyanant (E-mail: vteerasit@gmail.com)
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Abstract

SMARCA4-deficient sinonasal carcinoma a subtype of SWI/SNF complex–deficient sinonasal carcinomas is a rare, highly aggressive sinonasal malignancy with only 23 cases reported in the literature to date. We present a case of a 70-year-old woman referred to our institution with a preliminary diagnosis of small cell neuroendocrine carcinoma. A computed tomography revealed a nasal cavity mass extending into the sphenoid sinus and nasopharynx, without involvement of the skull base, pterygoid, or orbit. Histologic examination revealed monomorphic, large, undifferentiated neoplastic cells that showed loss of SMARCA4 expression. SMARCA4-deficient sinonasal carcinoma is a rare malignant neoplasm with an aggressive clinical course and poor prognosis. Diagnosis typically relies on a combination of histologic findings and immunohistochemical staining to identify this high-grade malignancy.

Keywords: SMARCA4, BRG1, SWI/SNF complex-deficient sinonasal carcinoma

บทคัดย่อ

มะเร็งโพรงจมูกชนิด SMARCA4-deficient sinonasal carcinoma เป็นชนิดย่อยของมะเร็งโพรงจมูกในกลุ่ม SWI/SNF complex–deficient sinonasal carcinomas มะเร็งชนิดดังกล่าวพบได้ยากและมีการดำเนินโรคที่รุนแรง โดยปัจจุบันมีรายงานผู้ป่วยเพียง 23 รายทั่วโลก รายงานผู้ป่วยรายนี้เป็นผู้หญิงอายุ 70 ปี ที่ถูกส่งตัวมาที่โรงพยาบาลของเรา โดยได้รับการวินิจฉัยเบื้องต้นว่าเป็นมะเร็งโพรงจมูกชนิด small cell neuroendocrine carcinoma การตรวจภาพทางรังสีวิทยาด้วยเครื่อง computed tomography พบเนื้องอกในโพรงจมูกลุกลามไปที่ไซนัสฐานสมอง (sphenoid sinus) และ คอหอยหลังโพรงจมูก (nasopharynx) โดยที่ยังไม่ไปถึงกระดูกฐานกะโหลก (skull base) กระดูกเทอริกอยด์ (pterygoid bone) หรือเบ้าตา การตรวจทางจุลพยาธิวิทยาพบเซลล์มะเร็งที่มีขนาดใหญ่ที่ไม่มีการเปลี่ยนสภาพของเซลล์และไม่เกิดปฏิกิริยาอิมมูโนฮิสโตเคมีกับ SMARCA4 มะเร็งโพรงจมูกชนิด SMARCA4-deficient sinonasal carcinoma เป็นมะเร็งที่พบได้ยากมีการดำเนินโรคที่รุนแรงและมีพยากรณ์โรคที่ไม่ดี แนวทางการวินิจฉัยต้องใช้การตรวจทางจุลพยาธิวิทยาร่วมกับอิมมูโนฮิสโตเคมี

คำสำคัญ: SMARCA4, BRG1, มะเร็งโพรงจมูกชนิด SWI/SNF complex-deficient sinonasal carcinoma

Introduction

The sinonasal tract is recognized for its diversity of neoplasms, many of which share overlapping

histologic and immunohistochemical features. SWI/SNF complex–deficient sinonasal carcinoma represents a subset of highly aggressive sinonasal malignancies; they constitute 1%-3% of sinonasal carcinomas and 3%-20% of tumors diagnosed as sinonasal undifferentiated carcinoma.[1] These tumors are characterized by poorly differentiated to undifferentiated carcinoma with the loss of one SWI/SNF complex subunit (SMARCB1 or SMARCA4) and a lack of distinctive histologic features to classify them into another specific entity.[2] SMARCA4-deficient sinonasal carcinoma is a rare subtype of SWI/SNF complex–deficient sinonasal carcinomas, with only 23 cases reported in the literature to date.[3-7] We herein present a case of a 70-year-old woman referred to our institution with a preliminary diagnosis of small cell neuroendocrine carcinoma to emphasize histologic and immunohistochemical findings of SMARCA4-deficient sinonasal carcinoma.

Case report

A 70-year-old woman with a medical history of diabetes mellitus, dyslipidemia, and hypertension was referred to our institution for evaluation of a nasal mass. She presented with epistaxis and nasal congestion for 2 months. The patient had no family history of malignancy and no smoking history. Clinical examination revealed an ulcerative mass completely occluding the right nostril. There was no cervical lymphadenopathy. A computered tomography of the paranasal sinuses showed a nasal cavity mass extending into the sphenoid sinus and nasopharynx, without involvement of the skull base, pterygoid, or orbit. A biopsy obtained from the referring hospital where a diagnosis of small cell neuroendocrine carcinoma was rendered.

Resection was performed at our institution. Histologic examination revealed unremarkable sinonasal mucosa with underlying monomorphic, large, undifferentiated tumor cells with scant pale eosinophilic cytoplasm, arranged in lobular, nests, and solid sheets with focal areas of abortive rosettes formation. Tumor necrosis, brisk mitotic activity, and apoptotic figures were observed. Rhabdoid features and surface epithelial dysplasia were not observed. Immunohistochemically, the tumor cells showed focal expression of pan cytokeratin AE1/AE3, calretinin, and p16, but were negative for p63, S100 protein, desmin, CD99, NKX2.2, and NUT. Epstein Barr virus in situ hybridization (EBER) was negative. Weak and focal staining for CD56 and synaptophysin expression was weak and focal, while chromogranin A staining was completely negative. The tumor cells show intact expression of SMARCB1 (INI1) but loss of expression of SMARCA4 (BRG4). The diagnosis of SMARCA4-deficient sinonasal carcinoma was made. The patient underwent induction chemotherapy followed by radiation therapy.

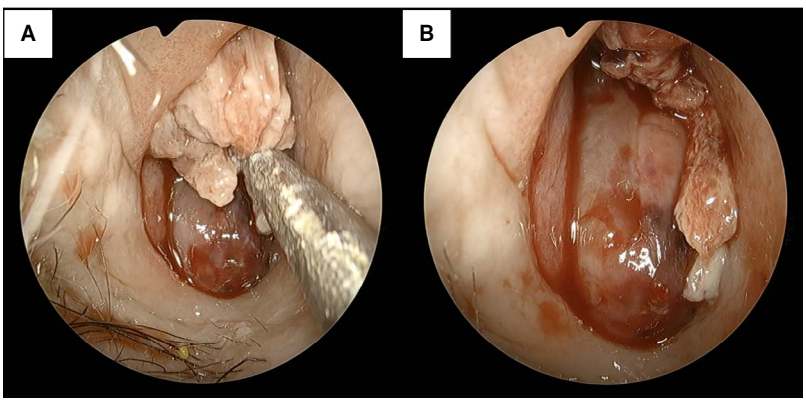

Figure 1. (A) Sinuscope reveals an ulcerative mass covered with fibrin. (B) The ulcerative mass completely occludes the right nostril.

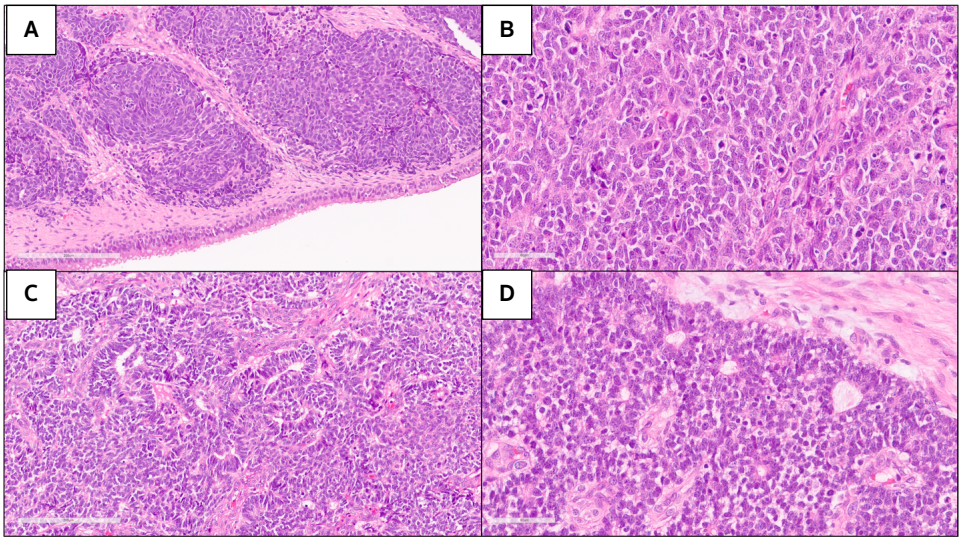

Figure 2. (A) SMARCA4-deficient sinonasal carcinoma growing beneath benign surface respiratory epithelium without dysplasia. (B) Higher magnification showing monomorphic, medium-to-large sized, undifferentiated neoplastic cells with scant pale eosinophilic cytoplasm arranged in solid sheets. (C-D) Tumor showing focal abortive rosettes formation.

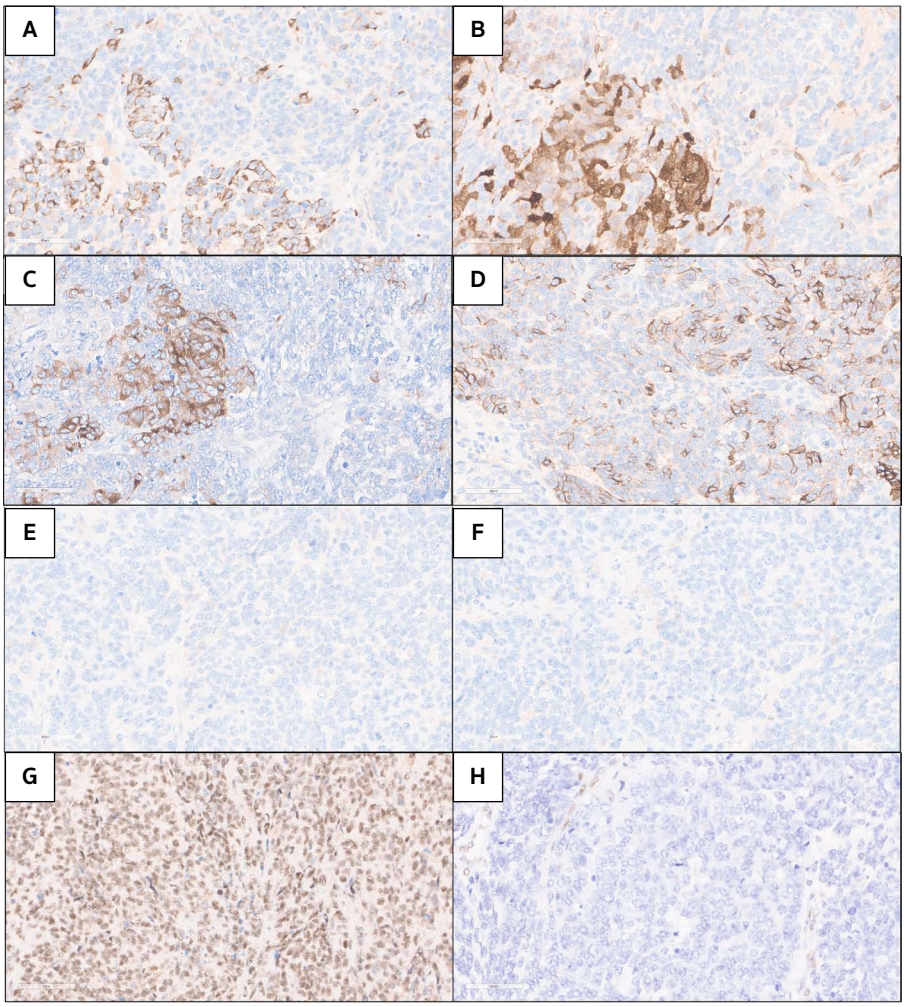

Figure 3. Tumor cells are focally positive for AE1/AE3 (A), p16 (B), synaptophysin (C), CD56 (D) and negative for chromogranin A (E), p63(F). INI1 (SMARCB1) expression is intact (G), but BRG1 (SMARCA4) expression is completely lost of nuclear (H).

Discussion

The SWI/SNF complex is involved in chromatin remodeling, which affects cell transcriptional regulation. Inactivating alterations in SWI/SNF complex components can lead to aberrant gene expression and tumor progression, and are found in a wide range of cancers, including both solid tumors and hematologic malignancies across different organs.[8] The SMARCA4 gene is a central component of the SWI/SNF complex and functions as a tumor suppressor gene.[9]

SMARCA4-deficient sinonasal carcinoma was first described by Agaimy and Weichert in 2017 and is classified as a subtype of SWI/SNF complex-deficient sinonasal carcinoma in the 5th edition of the WHO Classification of Head and Neck Tumours.[2-3] This carcinoma is rare, comprising less than 1% of all sinonasal carcinomas, and represents approximately 9% of all sinonasal undifferentiated carcinoma-like tumors.[6, 10] It predominantly affects males, with patients typically aged between 20 and 70 years, and shows a predilection for the nasal cavity.[5, 10] Clinically, it often presents as an advanced lesion, frequently classified as a T4 stage tumor.[4] The prognosis is poor, with median survival of 11.5 months.[5]

Histologically, SMARCA4-deficient sinonasal carcinoma is characterized by sheets of large, epithelioid, anaplastic cells, with a variable nested or trabecular pattern. A small number of cases may exhibit a basaloid small cell pattern and abortive neuroendocrine-like rosettes, although rhabdoid cells are uncommon. Brisk mitotic activity and extensive foci of necrosis are commonly observed. These features are non-specific and can be observed in many high-grade sinonasal neoplasms. Nevertheless, all cases of SMARCA4-deficient sinonasal carcinoma show positivity for pan cytokeratin AE1/AE3, variable positivity for CK7, and focal positivity for neuroendocrine markers. CK5, p63, p40, p16, and NUT immunohistochemistry are negative. A characteristic feature is the absence or diminished expression of SMARCA4 (BRG1) in the majority of the tumor cells, while SMARCB1 (INI1) expression is retained in all cases.[11]

The differential diagnosis of SMARCA4-deficient sinonasal carcinoma can be challenging and requires ancillary testing to exclude other tumors with undifferentiated cell morphology such as NUT carcinoma, neuroendocrine carcinoma, high-grade olfactory neuroblastoma, IDH-mutant sinonasal undifferentiated carcinoma, lymphoepithelial carcinoma, Ewing sarcoma family tumors, and SMARCB1-deficient sinonasal carcinoma. It is important to note that all these neoplasms typically retain SMARCA4 (BRG1) expression. Teratocarcinosarcoma is another rare and highly aggressive malignant neoplasm in the sinonasal tract characterized by the absence of SMARCA4 (BRG1) expression. It exhibits a triphasic growth pattern comprising teratoma-like component, carcinoma-like component, and sarcomatous stromal/mesenchymal components, often with highly variable neuroectodermal-like features.[11] Variable expression of neuroendocrine markers can lead to misdiagnosis, as demonstrated in our case[12]. The morphology of SWI/SNF complex-deficient sinonasal carcinomas can resemble that of neuroendocrine carcinoma. However, since SWI/SNF complex–deficient sinonasal carcinoma is a molecularly defined entity, the loss of SMARCB1 (INI1) or SMARCA4 (BRG1), combined with undifferentiated morphology, is sufficient for making a diagnosis of this entity.

Diagnosis of SMARCA4-deficient sinonasal carcinoma can be difficult due to its rarity, and the histomorphology exhibits non-specific patterns that can mimic other high-grade sinonasal tract

neoplasms. When faced with high-grade sinonasal tract neoplasms exhibiting poorly or undifferentiated morphology, the first step is to classify whether the tumor is a carcinoma or a non-carcinoma. Pan cytokeratin may be helpful in this step but should be used with caution, as some sarcomas and other non-epithelial neoplasms may show aberrant expression of pan cytokeratin. In the case of confirming carcinoma, squamous markers such as CK5/6, P40, and P63 are the second step, since poorly differentiated squamous cell carcinoma, lymphoepithelial carcinoma, NUT carcinoma, and some SMARCB1-deficient carcinomas are reactive to these markers. If tumors are reactive to squamous markers, additional testing such as P16, HPV testing, EBER, NUT, and SMARCB1 should be conducted. In cases that are non-reactive to squamous markers, neuroendocrine carcinoma, SMARCB1-deficient carcinoma, SMARCA4-deficient carcinoma, and sinonasal undifferentiated carcinoma should be included in the differential diagnosis. Additionally, further testing such as neuroendocrine markers (chromogranin A, synaptophysin, CD56, INSM1), SMARCB1 (INI1), SMARCA4 (BRG1), and IDH mutation testing should be considered. The diagnosis of sinonasal undifferentiated carcinoma should not be rendered until other high-grade sinonasal tract neoplasms have been excluded.

Without the use of SMARCB1 (INI1) and SMARCA4 (BRG1), the diagnosis of SWI/SNF complex–deficient sinonasal carcinoma, such as SMARCB1-deficient sinonasal carcinoma and SMARCA4-deficient sinonasal carcinoma, cannot be rendered. SMARCA4-deficient sinonasal carcinoma may be underreported. In the past, when SMARCB1 (INI1) and SMARCA4 (BRG1) were not utilized, these cases have been diagnosed as neuroendocrine carcinoma, poorly differentiated carcinoma/malignant tumor, olfactory neuroblastoma, teratocarcinosarcoma, and sinonasal undifferentiated carcinoma.[4-5] For this reason, SMARCB1 (INI1) and SMARCA4 (BRG1) should be included in a panel of immunohistochemical studies when evaluating poorly or undifferentiated carcinomas of the sinonasal tract, especially before making the diagnosis of sinonasal undifferentiated carcinoma and neuroendocrine carcinoma.

Due to its recent recognition as a distinct entity, there is no standard treatment for SMARCA4-deficient sinonasal carcinoma. However, current management typically involves a combination of surgical resection, chemotherapy, and radiotherapy, similar to other high-grade carcinomas of the sinonasal tract. Surgical resection remains a major component of treatment along with radiation therapy and chemotherapy. The current gold standard for surgical treatment is endoscopic endonasal or craniofacial resection. An essential part of the treatment is radiation therapy. When compared to conventional radiotherapy (CRT), intensity-modulated radiation therapy (IMRT) with doses of at least 60 Gy has been associated with improved overall survival. Systemic chemotherapy is almost always included in the treatment regimen, typically using cisplatin, etoposide, 5-FU, docetaxel, and paclitaxel.[13] Although there is no specific treatment regimen established at present, EZH2 and CDK4/6 inhibitors and checkpoint inhibitors may offer potential benefits.[11] Further research is needed to fully determine their efficacy.

Conclusion

SMARCA4-deficient sinonasal carcinoma is a rare neoplasm with an aggressive clinical course and poor prognosis. Diagnosis typically relies on a combination of histologic features and immunohistochemical findings (loss of SMARCA4 expression) to identify this high-grade malignancy.

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