

## Case Report

# SMARCB1 (INI1)-deficient sinonasal carcinoma: a newly described entity

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**Abstract:** SMARCB1 (INI1)-deficient sinonasal carcinoma is a recently described variant of sinonasal tract carcinoma characterized by complete loss of nuclear SMARCB1 (INI1). It is very rare and currently underdiagnosed because of a lack of awareness. Before the description of SMARCB1 (INI1)-deficient sinonasal carcinomas, these tumors were probably misclassified as various malignant neoplasms. To date, only 16 cases have been reported in the English literature. The authors herein report an additional case of SMARCB1 (INI1)-deficient sinonasal carcinoma of the maxillary sinus. An 86-year-old man presented with a painless, progressively enlarging mass on the left palate and intermittent epistaxis. Computed tomography displayed a large mass occupying the entire left maxillary sinus with destruction of maxillary bone and involvement of the left nasal cavity. The patient underwent radical left maxillectomy. The postoperative pathological diagnosis was sinonasal undifferentiated carcinoma. Immunohistochemistry for SMARCB1 (INI1) confirmed complete loss of nuclear SMARCB1 (INI1) expression in tumor cells, and the diagnosis of SMARCB1 (INI1)-deficient sinonasal carcinoma was finally established. With increased awareness and the use of SMARCB1 (INI1) immunohistochemistry, more SMARCB1 (INI1)-deficient carcinomas will be identified, leading to a more complete understanding of its pathologic and clinical features.

**Keywords:** SMARCB1, INI1, sinonasal carcinoma, maxillary sinus

## Introduction

SMARCB1, known as INI1, hSNF5, BAF47, is a tumor suppressor gene located on chromosome 22q11.2. Its gene product SMARCB1 (INI1) is a core subunit of the SWI/SNF ATP-dependent chromatin remodeling complex. SMARCB1 (INI1) is ubiquitously expressed in nuclei of all normal tissues and plays a critical role in development and tumor suppression [1]. SMARCB1 inactivating mutations were initially found to be associated with malignant rhabdoid tumors. In addition, the prototypical group of SMARCB1-deficient neoplasms includes also epithelioid sarcomas (both proximal and distal types), renal medullary carcinomas, as well as a subset of myoepithelial carcinomas, epithelioid malignant peripheral nerve sheath tumors, extraskeletal myxoid chondrosarcomas, and other rare neoplasms [2].

SMARCB1 (INI1)-deficient sinonasal carcinoma is a recently described variant of sinonasal

tract carcinoma characterized by basaloid/rhabdoid tumor morphology and complete loss of nuclear SMARCB1 (INI1) [3, 4]. It is very rare and currently underdiagnosed because of a lack of awareness. Before the description of SMARCB1 (INI1)-deficient sinonasal carcinomas, these tumors were probably misclassified as various malignant neoplasms [3-5]. To date, only 16 cases have been reported in the English literature [3-5]. The authors herein report an additional case of SMARCB1-deficient sinonasal carcinoma of the maxillary sinus in an 86-year-old man, which was originally diagnosed as sinonasal undifferentiated carcinoma.

## Case report

In May 2013, an 86-year-old man was referred to our department with a 4-month history of a painless, progressively enlarging mass on the left palate and a 3-month history of intermittent epistaxis. The patient was a non-smoker, but

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**Figure 1.** Axial CT image shows a large lesion occupying the entire left maxillary sinus with destruction of maxillary bone and involvement of the left nasal cavity.

regularly consumed alcohol (100 ml/day for 50 years). The medical and family histories were unremarkable. Intraoral examination revealed a firm, nontender, fixed mass (5 × 5 cm) on the left hard palate. The overlying mucosa was intact with normal color and consistency. There was no palpable cervical lymphadenopathy. Routine hematologic and biochemical examination, chest radiograph, and abdomen ultrasound appeared normal. Computed tomography (CT) displayed a large heterogeneously mass, measuring 5.8 × 6 × 6.8 cm in size, occupying the entire left maxillary sinus with destruction of maxillary bone and involvement of the left nasal cavity (**Figure 1**). An incisional biopsy was performed and a diagnosis of poorly differentiated carcinoma was made. The patient subsequently underwent a left radical maxillectomy. Further neck dissection and adjuvant radiotherapy and chemotherapy were not performed in consideration of the patient's age.

On microscopic examination, the tumor was composed of rounded and anastomosing nests of medium-sized basaloid and epithelioid cells, surrounded by thin to thick fibrovascular septa (**Figure 2A**). The neoplastic cells had indistinct cell membranes and exhibited moderate amounts of eosinophilic to amphophilic to clear cytoplasm (**Figure 2B** and **2C**). The nuclei were round, ovoid, or spindle-shaped, with vesicular

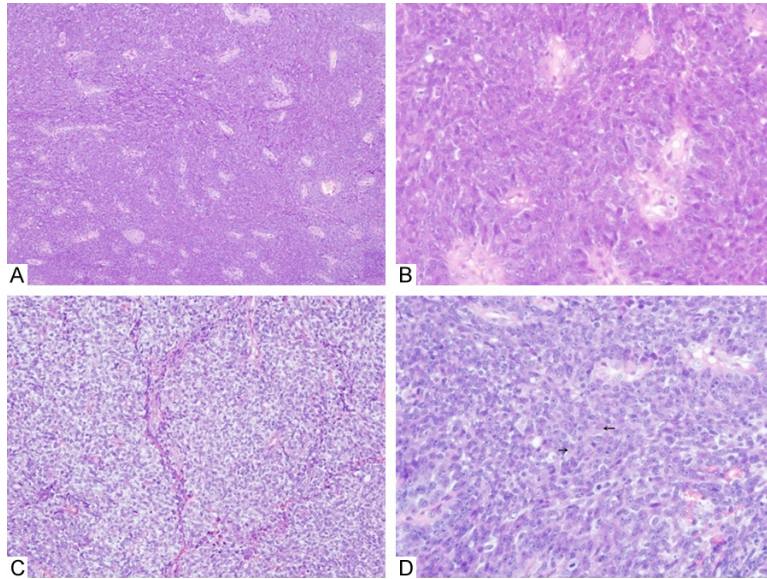
chromatin and inconspicuous to prominent nucleoli. Scattered rhabdoid cells with prominent eccentric eosinophilic cytoplasm were also recognized (**Figure 2D**). No evidence of squamous or glandular differentiation was observed. High mitotic activity was noted in some tumor regions. Areas of necrosis were also observed within the tumor. Immunohistochemically, the tumor cells showed strong diffuse reactivity for cytokeratin (CK) AE1/AE3 (**Figure 3A**). Fifty percentage of tumor cells displayed nuclear positivity for p63 and p40 (**Figure 3B**). Weak to moderate nuclear reactivity for p16 was present in 30% of tumor cells (**Figure 3C**). The tumor cells were negative for CK7, vimentin, S100, smooth muscle actin, calponin, synaptophysin, CD99, FLI-1 and NUT. In situ hybridization for EBV-encoded RNA was negative.

The postoperative pathological diagnosis was sinonasal undifferentiated carcinoma at that time. On the basis of morphologic similarity to SMARCB1 (INI1)-deficient sinonasal carcinoma reported in prior studies [3, 4], immunohistochemistry for SMARCB1 (INI1) was performed, which confirmed complete loss of nuclear SMARCB1 (INI1) expression in tumor cells (**Figure 3D**). The diagnosis of SMARCB1 (INI1)-deficient sinonasal carcinoma was finally established. The patient died of a biopsy-proven colonic adenocarcinoma 21 months later, but with no evidence of sinonasal disease recurrence.

### Discussion

Malignant sinonasal tract tumors are rare, with an estimated annual incidence of 0.5 to 1.0 per 100,000 in the United States population [6]. They represent approximately 3% of the head and neck malignancies and less than 1% of all malignant tumors [6]. Sinonasal malignancies encompass many histologic subtypes, with the majority being squamous cell carcinomas, followed by adenocarcinoma, melanoma and olfactory neuroblastoma. A wide variety of tumors occurring in the sinonasal tract may present with an undifferentiated or poorly differentiated morphology, being composed of small to medium and large, round or polygonal atypical cells. Overall, these lesions pose significant diagnostic difficulties for the surgical pathologist, especially in limited biopsy material. Nevertheless, precise tumor classification is required

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**Figure 2.** Histopathological findings. A. Low magnification shows anastomosing nests of tumor cells with basaloid features (hematoxylin-eosin,  $\times 100$ ); B. High magnification shows basaloid tumor cells with prominent nucleoli (hematoxylin-eosin,  $\times 200$ ); C. Nests of monomorphous tumor cells with clear cytoplasm are observed (hematoxylin-eosin,  $\times 200$ ); D. High magnification shows tumor cells with prominent nucleoli and high mitotic index. Scattered rhabdoid cells with prominent eccentric eosinophilic cytoplasm were noted (arrows) (hematoxylin-eosin,  $\times 400$ ).

for establishing prognosis and appropriate treatment strategies [7]. Currently recognized subtypes in the poorly differentiated/undifferentiated sinonasal carcinomas include basaloid squamous cell carcinoma, lymphoepithelial carcinoma, sinonasal undifferentiated carcinoma, small cell neuroendocrine carcinoma, poorly differentiated non-keratinizing squamous cell carcinoma, and NUT midline carcinoma [7]. Recently, a variant of sinonasal tract carcinoma characterized by complete loss of nuclear SMARCB1 (INI1) has been introduced by two independent groups, and the term SMARCB1 (INI1)-deficient sinonasal carcinoma has been proposed [3, 4].

The incidence of SMARCB1 (INI1)-deficient sinonasal carcinoma is difficult to ascertain, but it seems to be a very rare tumor. Agaimy et al identified 3 cases (2.7%) in a cohort of 112 sinonasal carcinomas [3]. Bishop et al found 7 cases (5%) among consecutive 140 sinonasal carcinomas, and 2 additional consultation cases [4]. Bell et al identified 4 cases (1.7%) among 230 primary sinonasal tumors [5]. Together with our case, there are only 17 cases of SMARCB1-deficient sinonasal carcinoma at the moment [3-5]. Ten tumors (72%) occurred in

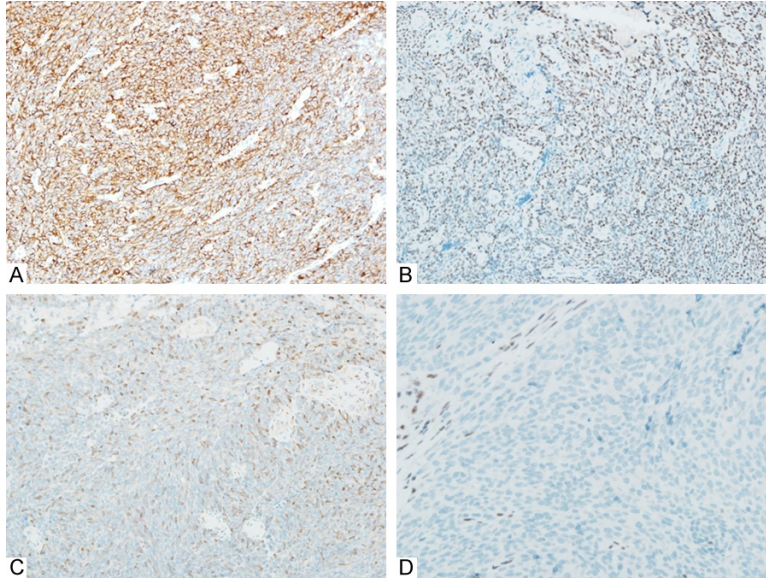
women, and 7 tumors (28%) occurred in men. The reported mean age at presentation was 56 years (range, 28-86 years). The 86-year-old male in the present study appears to be the oldest patient reported so far. Most patients presented with symptoms including epistaxis, headaches, eye symptoms (e.g., proptosis, tearing, and visual disturbances), nasal obstruction, sinusitis or facial pain. The most common specific site of origin was the ethmoid sinus, followed by the nasal cavity. But most patients presented as large tumors involving multiple sinonasal tract sites, even with invasion of the orbit, skull base or brain. Fourteen (82% of patients) had T4 disease; two had T3 disease and one had T2 disease. At the time of presentation, one patient had nodal

disease and none of the patients had distant metastases. Follow-up information was available for 16 cases, with an average period of 34.8 months and ranging from 3 to 102 months. Recurrence was reported in 7 cases (43.8%). Cervical lymph node metastases were reported in 3 cases (18.8%). Distant metastases were reported in 4 cases (25%). Six patients (37.5%) died of disease at 15, 25, 29, 30, 24, and 102 months. Three patients (18.8%) were alive with disease at 12, 33 and 70 months, respectively. Seven patients (43.75%) were without any evidence of disease after a mean of 31 months (range, 3-84 months), who were either alive (5 patients) or had died of other causes (2 patients). Although the number of reported cases is limited, these data indicate that SMARCB1 (INI1)-deficient sinonasal carcinoma is an aggressive malignancy with poor prognosis.

Histologically, SMARCB1 (INI1)-deficient sinonasal carcinomas typically exhibit a solid architecture with tumor cells arranged in nests and sheets. A wide variety of morphologic tumor cell types, including basaloid, rhabdoid, oncocytoid, squamoid or spindled cell, have been iden-



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**Figure 3.** Immunohistochemical findings. A. The neoplastic cells were diffusely immunoreactive for CK AE1/AE3 ( $\times 200$ ); B. Fifty percentage of tumor cells displayed nuclear positivity for p63 ( $\times 200$ ); C. Weak to moderate nuclear reactivity for p16 were seen in 30% of tumor cells ( $\times 200$ ); D. SMARCB1/INI1 reactivity was absent in tumor cells but retained in endothelial cells ( $\times 400$ ).

tified [3-5, 8]. The basaloid cell is the predominant cell type in most cases. The rhabdoid cells vary greatly in their number and distribution. They are often scattered singly among the basaloid cells, but rarely predominant. The tumor cells usually have enlarged round nuclei with prominent nucleoli, and frequent mitosis. Necrosis is common. A prominent exophytic component with papillary fronds may be present. Peripheral palisading and radial growth around blood vessels imparting a pseudorosette-like pattern can be noted in some cases. True squamous or glandular differentiation is absent [3-5, 8].

Immunohistochemically, SMARCB1 (INI1)-deficient sinonasal carcinomas demonstrate an epithelial immunophenotype, with diffuse positivity for pancytokeratin and variable immunoreactivity for p63, p40 and CK5/6 [3-5]. Focal positivity for S100, vimentin, chromogranin and synaptophysin may be seen. CK7, actin, and NUT are negative. EBV in situ hybridization is negative [3-5]. Diffuse or partial p16 expression has been found to present in some cases, but high-risk HPV has not been detected in any of the carcinomas by DNA in situ hybridization or polymerase chain reaction analysis. SMARCB1 (INI1)-deficient sinonasal carcinomas characteristically demonstrate complete loss

of nuclear SMARCB1 (INI1) expression [3-5].

Based on recent advances in immunohistochemistry and molecular diagnostics, the current diagnostic strategy for undifferentiated tumors of the nasal cavities and paranasal sinuses has been proposed [7]. In general, these non-epithelial malignancies can be readily distinguished from undifferentiated carcinomas with the use of immunohistochemistry for CK, as well as other markers [7, 9, 10]. Classification of the undifferentiated carcinomas can be more challenging. The most important morphological differential diagnoses of SMARCB1 (INI1)-deficient sinonasal carcinomas include other poorly differentiated/

undifferentiated sinonasal carcinomas, especially basaloid squamous cell carcinoma and sinonasal undifferentiated carcinoma.

Lymphoepithelial carcinoma and nasopharyngeal carcinomas of undifferentiated type have morphologic features that may be helpful (indistinct cell borders, a syncytial appearance, and lymphoplasmacytic infiltrates), and EBV is detected in virtually 100% of cases while EBV has not been reported in SMARCB1 (INI1)-deficient sinonasal carcinomas. Small cell neuroendocrine carcinoma is composed of sheets or nests of closely packed cells with hyperchromatic nuclei, finely granular chromatin, inconspicuous nucleoli, and characteristic nuclear molding. Immunohistochemically, small cell neuroendocrine carcinoma is positive for neuroendocrine markers for chromogranin and synaptophysin, while SMARCB1 (INI1)-deficient sinonasal carcinoma is usually negative or focally positive. Basaloid squamous cell carcinoma is characterized by lobules of highly atypical basaloid cells with prominent peripheral palisading and frequent comedo-type necrosis. Squamous differentiation may not be readily apparent, especially in small biopsy specimens, making the separation from SMARCB1 (INI1)-deficient sinonasal carcinomas difficult. All 3 cases of SMARCB1 (INI1)-deficient sinonasal

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carcinomas reported by Agaimy et al were initially diagnosed as basaloid squamous cell carcinoma on the basis of the presence of basaloid epithelial cells with predominantly cohesive growth and peripheral palisading [3]. Distinguishing sinonasal undifferentiated carcinoma from SMARCB1 (INI1)-deficient sinonasal carcinoma can be very difficult, as both share many morphologic features, including large nuclei, prominent nucleoli, high mitotic rate, tumor necrosis, absence of true squamous differentiation and the absence of detectable high-risk human papillomavirus DNA or Epstein-Barr virus [7]. Actually, SMARCB1 (INI1)-deficient sinonasal carcinomas accounted for 14% of those tumors that had been originally diagnosed as sinonasal undifferentiated carcinoma in the report by Bishop et al [4]. The presence of rhabdoid cells is the most important finding that raises the suspicion of SMARCB1 (INI1)-deficient sinonasal carcinoma. However, the degree of rhabdoid differentiation was highly variable. Most cases displayed very subtle rhabdoid cells that may be hardly detectable [3-5]. Use of SMARCB1 immunohistochemistry is an easy way to recognize this entity and separate it from other poorly differentiated/undifferentiated sinonasal carcinomas.

In conclusion, SMARCB1 (INI1)-deficient sinonasal carcinoma is a rare, underdiagnosed and distinctive entity with propensity for advanced-stage presentation and poor prognosis. When dealing with poorly differentiated/undifferentiated sinonasal carcinomas, especially with basaloid or rhabdoid features, a high degree of suspicion of SMARCB1 (INI1)-deficient sinonasal carcinoma should be maintained. The use of SMARCB1 (INI1) immunohistochemistry is mandatory in arriving at the accurate diagnosis. With increased awareness and the use of SMARCB1 immunohistochemistry, more SMARCB1 (INI1)-deficient carcinomas will be identified, leading to a more complete understanding of its pathologic and clinical features.

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### Disclosure of conflict of interest

None.

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