

# SMARCB1-Deficient Sinonasal Carcinoma: A Case Report and Discussion of the Clinical Implications

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## Abstract

**Objective:** SMARCB1-deficient sinonasal tract carcinomas are an emerging subset of rare tumors recently described in the literature, with less than 100 reported cases. Given the aggressive nature of this tumor, timely diagnosis is especially important. We present a case report of a SMARCB1-deficient carcinoma of the sinonasal tract.

**Methods:** Case report with review of the literature.

**Results:** The patient was a 53-year-old male with computed tomography (CT)-proven mass of the right ethmoid and sphenoid sinuses. Rigid nasal endoscopy revealed a purple mass completely obstructing the right nasal cavity that extended inferiorly from the posterior ethmoids and sphenoid sinuses. Initial biopsy in the emergency room was nondiagnostic due to extensive tumor necrosis. Magnetic resonance imaging (MRI) revealed T2 hypointense enhancing mass centered in the right posterior ethmoids with invasion into the right orbital apex, classifying it as a T4b tumor. The patient underwent repeat biopsy with frozen section and tumor debulking. Immunohistochemical analysis of subsequent biopsy revealed complete loss of INI-1 and negative staining for other pertinent markers, alluding to the diagnosis of SMARCB1-deficient sinonasal tract carcinoma.

**Conclusion:** Tumor necrosis may be problematic in obtaining a diagnosis for SMARCB1-deficient sinonasal carcinomas. Thus, sampling various regions of the tumor during initial biopsy can prevent delays in diagnosis and treatment.

## Keywords

SMARCB1, sinonasal tract malignancy, sinonasal undifferentiated carcinoma, nasal cavity malignancy, paranasal sinus malignancy, INI-1 deficient

Sinonasal tract tumors account for 3% to 5% of all head and neck cancers, with squamous cell carcinomas being the most common pathology seen.<sup>1</sup> The recently discovered group of SMARCB1 (INI-1)-deficient sinonasal carcinomas has been an area of growing interest and research. This group of sinonasal tract tumors was first described in the literature in 2014, with the most recent report on a series of 39 total cases further defining SMARCB1-deficient sinonasal carcinoma as an emerging class of tumor subtype.<sup>2,3</sup> These tumors typically present with locally advanced disease and have high rates of morbidity and mortality, necessitating a timely diagnosis and intervention.<sup>3</sup> Patients typically present with symptoms of eye pain, blurry vision, nasal obstruction, and headaches.<sup>2</sup> Imaging findings of bony infiltration, especially when there is calcification and periosteal reaction such as “hair on end” spikes, are particularly concerning for SMARCB1-deficient tumors.<sup>4</sup> Invasion occurs most commonly to the associated orbit and anterior cranial fossa.<sup>4</sup> Grossly, these carcinomas tend to contain areas of tumor necrosis and

frequently invade into adjacent bone.<sup>5</sup> Histologically, these tumors are poorly or undifferentiated and lack any histologic evidence of specific cellular differentiation (eg, squamous, glandular, other). They are primarily comprised of basaloid cells with occasional scattered rhabdoid cells.<sup>3</sup> Immunohistochemical evaluation reveals a complete absence of immunostaining for SMARCB1 (INI-1), a tumor suppressor gene on chromosome 22q11.2 that is expressed in the nuclei of all normal cells.<sup>5</sup>

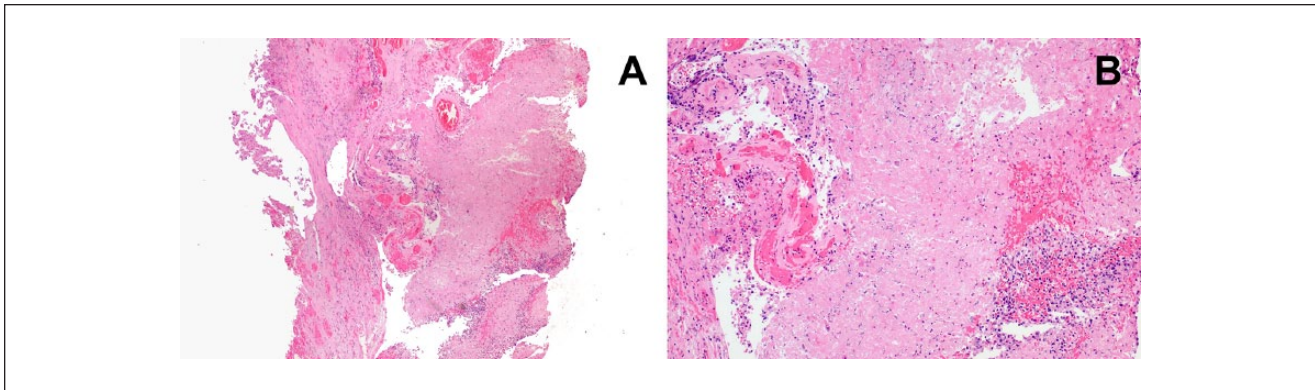
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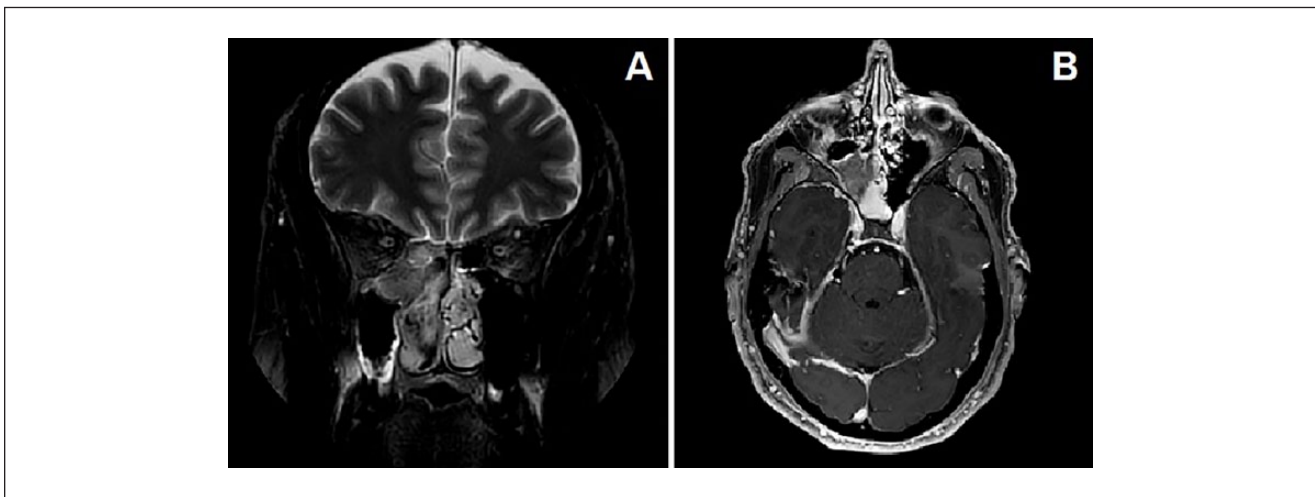
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**Figure 1.** (A, B) Initial biopsy showing tumor necrosis and lack of viable tumor cells (hematoxylin and eosin, original magnification: A =  $\times 40$ , B =  $\times 100$ ).



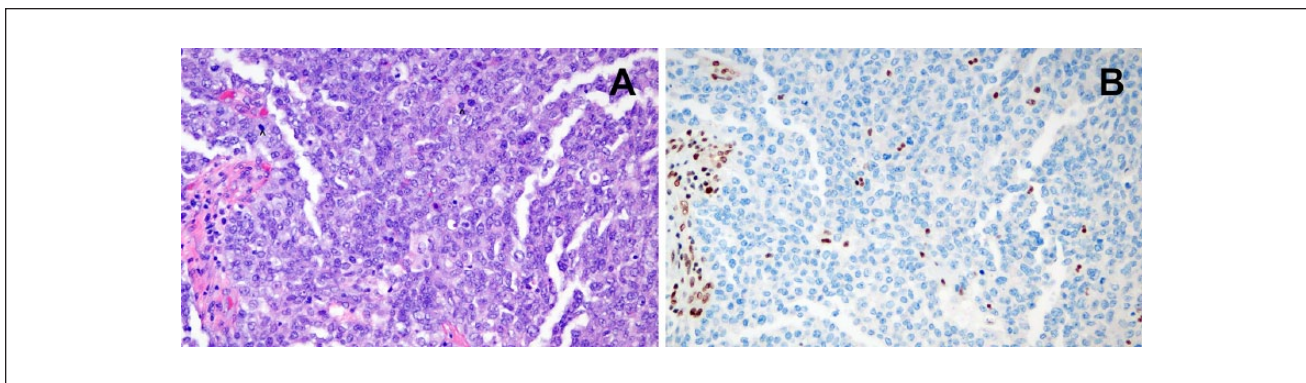
**Figure 2.** (A, B): Preoperative magnetic resonance imaging (A) T2 coronal image. (B) T1 axial post contrast image showing the mass based in the posterior ethmoids invading the orbital apex

Given the necessity of timely diagnosis for this carcinoma, high clinical suspicion along with a good tissue sample is of utmost importance. We present a case of SMARCB1-deficient sinonasal carcinoma to increase understanding and familiarity with this disease process in the otolaryngology literature.

### Case Report

A 53-year-old male presented with a 2-day history of right-sided epistaxis and a 5-week history of right-sided nasal obstruction to the emergency department. He had been initially treated with 7 days of antibiotics for presumed sinus infection by his primary care provider, but his symptoms failed to resolve, and he presented for reevaluation. Contrast-enhanced computed tomography (CT) scan of the sinuses was performed and demonstrated a partially enhancing mass that completely opacified the

right sphenoid and posterior ethmoid air cells with dehiscence of the lateral nasal wall involving the pterygopalatine fossa and extraconal fat in the posterior orbit. After applying topical decongestion and anesthesia with cophonylaine-soaked pladgets, rigid nasal endoscopy was performed. On endoscopy, a soft, purple mass was visualized completely obstructing the right nasal cavity that appeared to be extending inferiorly from the posterior ethmoids and sphenoid sinuses. A 0.8 cm biopsy was taken in the emergency room. The results from this initial biopsy showed necrotic, inflammatory, and fibrinous debris without viable appearing material to further evaluate (Figure 1). Magnetic resonance imaging (MRI) of the head with gadolinium was obtained to better characterize the mass. The MRI showed a T2 hypointense enhancing mass centered in the right posterior ethmoids measuring  $2.5 \times 2.6 \times 2.3$  cm with invasion into the right orbital apex, thus classifying it as a T4b tumor (Figure 2).



**Figure 3.** (A) High-grade malignant basaloid cells with vesicular chromatin, prominent nucleoli, and high mitotic rate indicated by  $\wedge$  (hematoxylin and eosin, original magnification  $\times 200$ ). (B) Tumor cells showing loss of INI-1 immunohistochemical staining and retained staining for INI-1 in background inflammatory cells and benign vessels (original magnification  $\times 200$ ).

Due to the initial nondiagnostic biopsy and difficult endoscopic exam, the patient was taken to the operating room for a planned repeat biopsy with frozen section and tumor debulking using image guidance. Intraoperatively, the tumor was found to be extensively invading the sphenoid and ethmoid sinuses with erosion of the lamina papyracea. The tumor was excised back to the orbital apex through the ethmoids and the orbitocarotid recess in the sphenoid sinus. The final histology showed a poorly differentiated carcinoma comprised predominantly of basaloid cells with conspicuous nucleoli and rare rhabdoid cells with eccentrically located nuclei and increased eosinophilic cytoplasm. Areas of abundant necrosis and associated desmoplasia were also noted. Immunohistochemical analysis revealed the tumor cells to be strongly positive for pancytokeratin AE1-AE3, p63, p40, with complete loss of INI-1 (Figure 3). These findings raised the possibility of SMARCB1(INI-1)-deficient sinonasal carcinoma; however, as this is a diagnosis of exclusion, other pertinent entities in the differential diagnosis, including nasopharyngeal carcinoma, p16 associated non-keratinizing squamous cell carcinoma, rhabdomyosarcoma, NUT midline carcinoma, melanoma, and large cell neuroendocrine carcinoma, were excluded due to negative immunohistochemical staining for pertinent markers. Given the presence of locally advanced disease with bone involvement and lack of metastatic disease at the time of initial presentation, the patient was pathologically staged as pT4bN0M0 using the American Joint Committee on Cancer Staging Manual.

Postoperative contrast-enhanced CT of the neck showed a  $5 \times 6 \times 5$  mm enhancing area of residual tumor in the right orbital apex and inferior orbital fissure with medial extension toward the sphenoid sinus and pterygopalatine fossa. Our patient completed induction chemotherapy with docetaxel, cisplatin, and fluorouracil, followed by concurrent chemoradiation with proton beam therapy. Local control was achieved from his treatment, but unfortunately, he

developed pulmonary metastases and died from widely metastatic disease 13 months after diagnosis.

## Discussion

The diagnosis of SMARCB1 (INI-1)-deficient sinonasal carcinoma is extremely rare, with less than 100 reported cases in the pathology literature. Data regarding the epidemiology, presentation, diagnosis, and prognosis of this disease process is limited. Due to the limited number of cases and knowledge of the entity, these tumors are still listed under the category of sinonasal undifferentiated carcinoma in the fourth edition of the World Health Organization classification of head and neck tumors.<sup>6</sup>

Most patients are middle aged at presentation (median age of 52) with a male predominance (23 males to 16 females) and present with nasal obstruction, headache, or vision change.<sup>3</sup> Due to the small number of reported cases, we are unable to determine the true demographics. Patients typically present at an advanced stage. Imaging showing an extensive nasal cavity or paranasal sinus mass with bony invasion should particularly raise suspicion for an aggressive tumor subtype, such as this. Segal et al<sup>7</sup> found preoperative biopsy in agreement with the final pathology in 86.9% of their study of unilateral nasal masses. Diagnosis with preoperative biopsy, however, may be difficult in these cases due to significant areas of necrosis. Our initial biopsy, although adequate in size (0.8 cm), was nondiagnostic due to significant edema of the nasal mucosa, posterior location, and patient discomfort despite topical anesthesia in this patient's case, making further bedside visualization and biopsy difficult. In our limited experience, it appears prudent to sample different areas of the tumor during initial biopsy to avoid potential delays in treatment.

Until recently, a specific marker to distinguish a subset of undifferentiated sinonasal tract malignancies has been lacking. The discovery of a histological marker for

SMARCB1 that is absent in 100% of cases greatly facilitates identification of this emerging tumor subtype.<sup>2</sup>

The current treatment algorithm for advanced sinonasal tumors includes surgical excision, with the addition of radiation or chemotherapy, depending on the completeness of resection and pathological features. The rare and heterogeneous nature of sinonasal malignancies has limited the availability and development of targeted therapies for these tumors.<sup>8</sup> The identification of SMARCB1 deficiency will not only likely aid in diagnosis of this tumor but importantly, will affect therapeutic options. SMARCB1 is a member of the SWI/SNF chromatin remodeling complex, which is mutated in up to 25% of all solid tumors.<sup>9</sup> Specifically, the SMARCB1 subunit is characterized as a tumor suppressor.<sup>9</sup> Loss of this subunit has been reported in malignant rhabdoid tumors, atypical teratoid rhabdoid tumors, and 90% of epithelioid sarcomas.<sup>10-18</sup> As a member of the BAF complex, SMARCB1 antagonizes the actions of the Polycomb Repressive Complex 2 (PRC2), resulting in decreased di- and tri-methylation of histone 3 at lysine 27 (H3K27me2, H3K27me3).<sup>19</sup> Thus, loss of SMARCB1 results in increased activity of PRC2 and silencing of genes involved in tumor suppression and differentiation.<sup>15,20-24</sup> Increased activity of Enhancer of Zeste Homolog 2 (EZH2), the catalytically active component of PRC2, appears to be essential for tumor development.<sup>25-27</sup> Two specific EZH2 inhibitors, EI1 and EPZ-6438, have shown promise in treating SMARCB1-deficient tumors.<sup>15</sup> In SMARCB1-mutant rhabdoid tumors, EI1 decreases H3K27me2 and H3K27me3 levels, and in EZH2-mutant cells, it inhibits cell growth and causes cell cycle arrest and apoptosis.<sup>28</sup> In mice carrying SMARCB1-mutant rhabdoid tumors, treatment with EPZ-6438 led to a decrease in H3K27me3 levels and dose-dependent tumor regression.<sup>29</sup> Given the promising findings of EZH2-inhibitors in treating other SMARCB1-deficient tumors in mouse models and patients in stage 2 trials, further studies are needed to investigate the efficacy of this therapy in SMARCB1-deficient sinonasal carcinomas. In the future, this may be a useful adjunctive treatment for patients with this disease in addition to surgical therapy.

## Conclusion

SMARCB1-deficient sinonasal tract carcinomas are a rare entity only recently described in the pathology literature. These tumors have a significant amount of necrosis, requiring aggressive biopsy techniques to expedite treatment. Going forward, targeted therapies aimed at these tumors may be helpful in improving patient outcomes, which makes diagnosis and awareness of this entity important. Currently, surgical therapy followed by chemoradiation for advanced disease is the mainstay of treatment.

Written informed consent was obtained from the patient to allow information and images to be published.

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