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SMARCB1(INI-1)-Deficient Sinonasal Carcinoma: An Evolving Entity

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Abstract

SMARCB1(INI-1)-deficient sinonasal carcinoma is a rare, poorly differentiated neoplasm with a poor prognosis. Though historically most were identified as sinonasal undifferentiated carcinoma, we now understand it to be a distinct entity. There is currently a general consensus supporting multimodal therapy, though the optimal sequence of surgery, chemotherapy, and radiation has yet to be defined.

Keywords

- sinonasal carcinoma
- SMARCB1
- INI-1
- SMARCB1(INI-1)-deficient
- sinonasal undifferentiated carcinoma
- SNUC
- SWItch/Sucrose non-fermentable
- SWI/SNF
- EZH2

Introduction

SMARCB1(INI-1)-deficient sinonasal carcinoma is a unique, rare neoplasm that had previously been categorized as a sinonasal undifferentiated carcinoma (SNUC). The current understanding is these tumors have distinct histologic and immunohistochemical patterns and result from a distinct genetic driving event. Substantially more research is necessary to better understand this entity and to define the optimal treatment approach.

Case Report

A 62-year-old male presented with several months of right nasal obstruction, epiphora, and headaches. He was a former smoker and had no other pertinent medical history. On exam, his extraocular movements were intact and he had tearing from the right eye. Otherwise, his cranial nerves were intact and symmetric bilaterally. On palpation, he had bilateral cervical lymphadenopathy. Rigid nasal endoscopy demonstrated tumor along the bilateral septum with what appeared to be potential submucosal spread on the right (►**Fig. 1**).

A computed tomography (CT) scan showed a mass within the right nasal cavity with erosion of the anterior ethmoid cells, expansion of the nasolacrimal duct, and extension into the medial right orbit. There was thinning of the right fovea ethmoidalis and lateral lamella, with areas of apparent osseous dehiscence and intracranial extension (►**Fig. 2**). Magnetic resonance imaging demonstrated a

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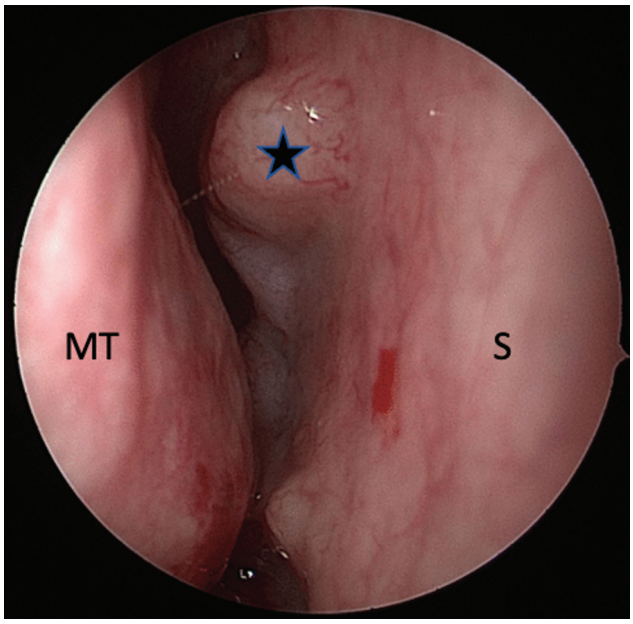

Fig. 1 Right nasal cavity mass (star). MT, middle turbinate; S, septum.

multilobulated enhancing mass involving the right greater than left superior nasal fossa with involvement of the nasal septum and extension into the floor of the anterior cranial fossa. There was mass effect on the right gyrus rectus and orbital gyrus without vasogenic edema. There was no involvement of the tissues of the orbit or extraocular muscles, but there was involvement of the nasolacrimal duct (►**Fig. 2**).

A biopsy was done in clinic and pathology showed a basaloid histologic pattern with nests of basophilic cells with high nuclear-to-cytoplasmic ratio growing in a desmoplastic stroma (►**Fig. 3**). The tumor cells on immunohistochemistry demonstrated a complete loss of SMARCB1(INI-1), which was retained within the normal stromal background cells (►**Fig. 4**).

A positron emission tomography/CT scan showed a fluorodeoxyglucose (FDG)-avid sinonasal mass, and bilateral FDG-avid cervical lymph nodes, with no evidence of distant metastasis. The patient was staged as a T4bN2cM0. The multidisciplinary tumor board recommended surgery followed by adjuvant chemoradiation.

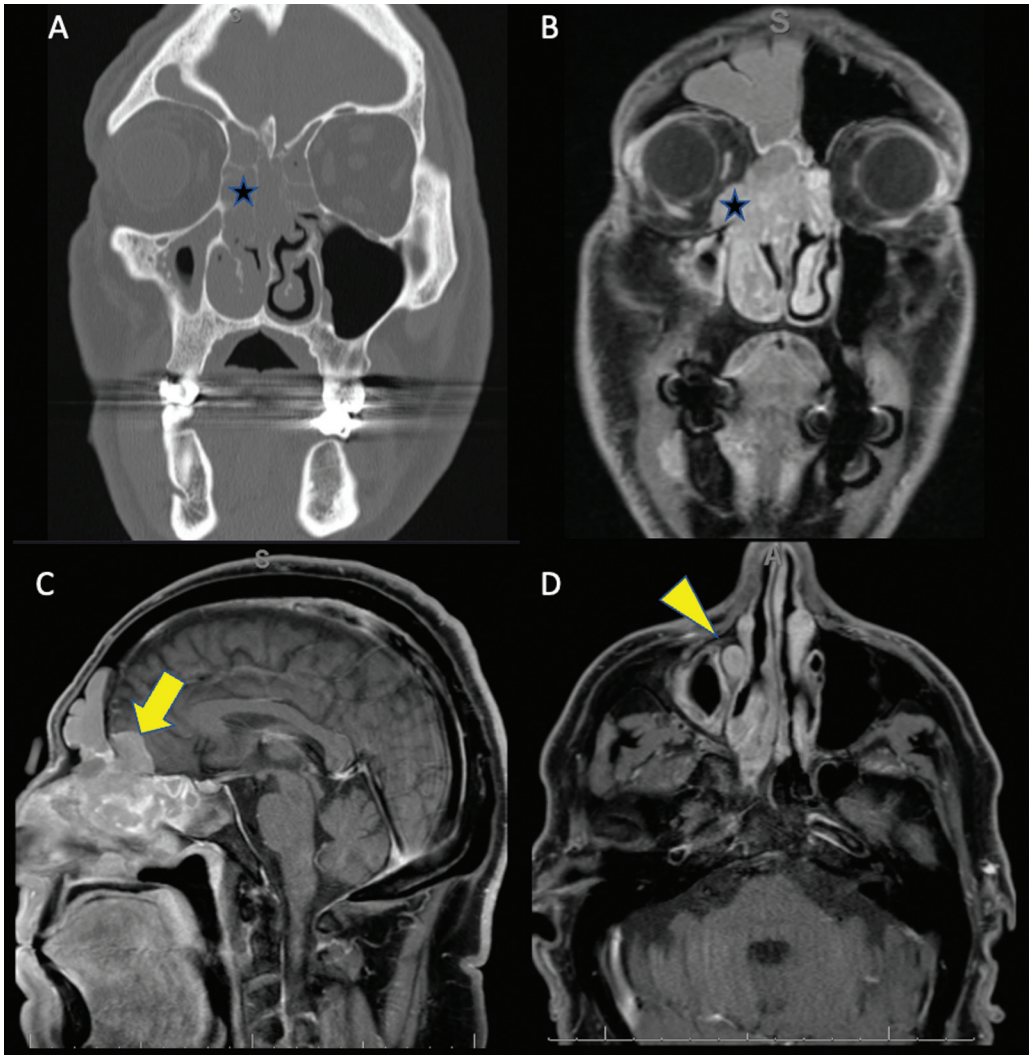

Fig. 2 Preoperative computed tomography (CT) (**A**) and magnetic resonance imaging (MRI) (**B–D**) images of right sinonasal mass with intraorbital extension (star), anterior cranial fossa extension (arrow), and nasolacrimal duct involvement (arrowhead).

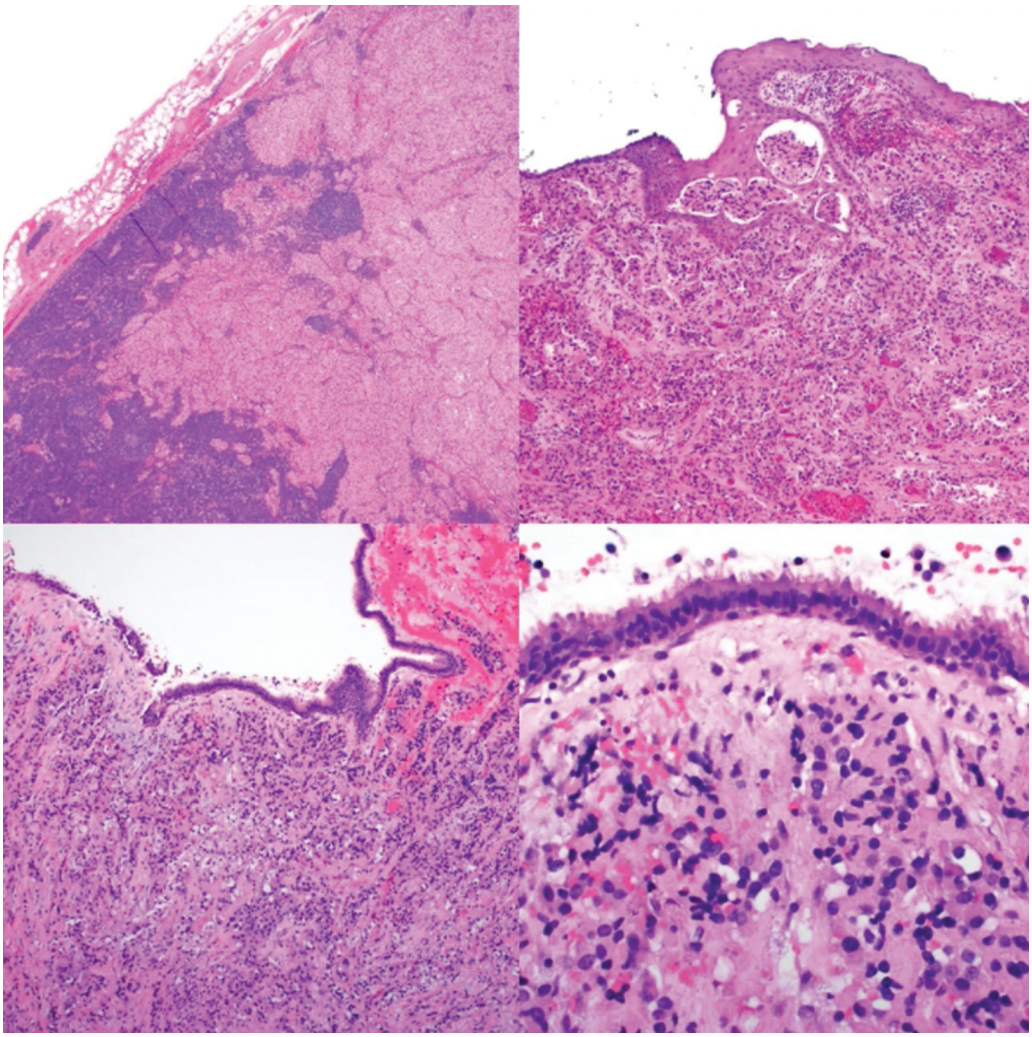

Fig. 3 Basaloid pattern with nests of basophilic cells with high nuclear-to-cytoplasmic ratio growing in a desmoplastic stroma.

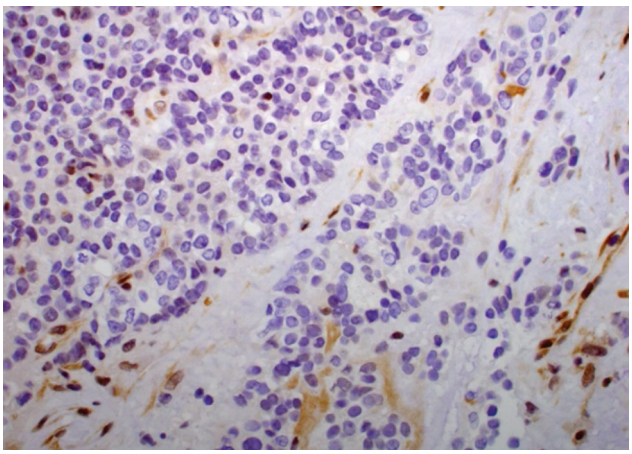

Fig. 4 Immunohistochemistry with a complete loss of SMARCB1 (INI-1), which was retained within the normal stromal background cells.

The patient underwent an endoscopic anterior skull base resection and gross total resection was achieved. In addition, he had a right dacryocystectomy. The skull base was reconstructed with Duragen and endoscopic pericranial flap. Bilateral neck dissections were also performed with several positive nodes bilaterally and in the retropharyngeal region. The right neck nodes showed extranodal extension (ENE) in all levels except for level IV. The patient was then treated with adjuvant chemoradiation. The primary site and the neck levels with ENE received 66 Gy, and the neck levels without ENE received 60 Gy. Concomitant cisplatin was given weekly for 6 doses. The patient is currently more than 24 months out from treatment and is without evidence of disease.

Literature Review

SNUC was historically thought to account for 3 to 5% of sinonasal carcinomas.[1] Recent advances in immunophenotyping of SNUCs have enabled further subtyping based on their genetic and expressive aberrations.[2] SNUC now actually represents a heterogeneous group of tumors with several new subclassifications. These include genuine SNUC, which shows IDH2 mutations and accounts for 49 to 82% of tumors formally diagnosed as SNUC. Other subtypes include NUT-midline carcinoma (accounting for 15% of former SNUC diagnoses), SMARCB1(INI-1)-deficient (14%), SMARCA4-deficient (9%),

human papillomavirus (HPV)-related SNUC, and adamantinoma-like Ewing family tumor.[3–5]

On histology, SMARCB1(INI-1)-deficient tumors show infiltrative margins, often with spread into the epithelium in a pagetoid manner. The surface epithelium always lacks conventional squamous dysplasia or carcinoma-in-situ. It shows cellular monotony, monomorphic small-to-medium sized rounded nuclei with dispersed chromatin, high mitotic rates, and necrosis.[2] There are various architectural subtypes, most commonly basaloid, followed by plasmacytoid, and then other rare variants. On immunohistochemistry, tumor cells show a complete loss of SMARCB1, which is retained in the normal stromal background cells (►**Fig. 4**).[2] In sinonasal tumors, this loss of SMARCB1 represents a distinctive neoplasm as opposed to transformation from a previously well-differentiated neoplasm, nor does it show squamous differentiation. It is negative for NUT, does not harbor HPV or Epstein–Barr virus, and is not seen in well-differentiated carcinomas.[2]

A mutation of SMARCB1, located on chromosome 22q11.3, is the primary driving genetic event in SMARCB1 (INI-1)-deficient tumors. SMARCB1 mutations are also observed in a variety of neoplasms outside of the sinonasal tract, including malignant or atypical teratoid or rhabdoid tumors of childhood, epithelioid sarcoma, and epithelial tumor entities in adults and the elderly.[2] SMARCB1 is an essential component of the SWItch/Sucrose non-fermentable (SWI/SNF) complex, which is responsible for several key functions, including regulation of cell differentiation, cell cycle control, and apoptosis.[6–8] The SMARCB1 gene acts as a tumor suppressor, and its absence alters SWI/SNF complex function, leading to increased EZH2 activity, which upregulates oncogenic pathways and suppresses tumor suppressor gene transcription.[9,10]

As this rare entity was first described in 2014, the literature on SMARCB1-deficient sinonasal carcinomas is quite limited. A systemic review and pooled analysis from Lee et al is the largest to date with 128 patients.[11] This study suggested that the clinical characteristics of SMARCB1-deficient sinonasal carcinoma closely mirror those of historic SNUC.[11] The median age was 53 years, and there was a predilection for the male sex.[11] Nodal metastasis was fairly rare (6%), and the majority of patients presented in later stages.[11] Six percent of patients presented with metastatic disease.[11]

Also due to the rarity of SMARCB1(INI-1)-deficient sinonasal carcinoma in the literature, not much is known about the optimal treatment approach. Lee et al reported that radical resection or surgery was performed in approximately 67% of patients.[11] Adjuvant treatment was frequently used (56%) while induction treatment was not (20%).[11] Multimodal treatment was used in 75% of patients, whereas 13% of patients received single-modality therapy.[11] Around 12% of patients' treatments could not be determined.[11] Univariate and multivariate analyses did not show any significant differences between induction treatment, adjuvant treatment, and multimodal treatment on overall survival.[11]

A literature review by Parsel et al described 69 patients with SMARCB1(INI-1)-deficient sinonasal carcinoma and showed similar findings, with the majority of patients undergoing surgical treatment (87%) followed by adjuvant treatment (88%).[12] Several different chemotherapeutic agents, including cisplatin, 5-fluorouracil, docetaxel, gemcitabine, and etoposide, were cited as used with varying degrees of success.[12]

Thus far in the literature, there is a general consensus for multimodal therapy; however, the optimal sequence of such has not yet been defined. Some authors advocate upfront surgery when resection is feasible, followed by chemoradiation. Other authors advocate for induction chemotherapy.[11] Similar to the current treatment of SNUC, if there is $>50\%$ response to induction chemotherapy, these authors recommend continuing chemoradiation. However, if there is $<50\%$ response to induction chemotherapy, then surgery followed by chemoradiation is recommended.

In regards to outcomes and survival, loss of SMARCB1(INI-1) expression portends a poorer prognosis compared with tumors in which SMARCB1 expression is retained.[13] There are higher rates of recurrence, higher rates of mortality, and significantly worse disease-free survival (8.5 vs. 31.8 months) in SMARCB1(INI-1)-deficient tumors.[12] SMARCB1 (INI-1)-deficient tumors have reported mortality rates of 37 to 56%, and median survival times of 22 to 39 months.[11–13] Later stage tumors (T4b) are associated with a worse prognosis.[11] Local, regional, and/or distant recurrence, with metastasis to the lungs, brain, pleura, bone, and liver, have all been described.[11]

Some future directions include prospective studies defining optimal management strategies and the sequence of multimodal therapy, and defining the efficacy of charged-particle therapy such as protons or carbon ions versus photons. Additionally, SMARCB-1(INI-1) loss could serve as the basis for novel therapeutics, and trials in nonsinonasal SMARCB1-deficient carcinomas are currently underway. Thus far, some have looked at immune checkpoint inhibitors, and others have evaluated tazemetostat, a potent EHZ2 inhibitor.[14,15]

Conclusion

SNUC represents a heterogeneous group of tumors, of which our understanding is continually evolving. Loss of SMARCB1 (INI-1) expression portends a poor prognosis. Future prospective studies are necessary to better define optimal management strategies and the sequence of multimodal therapy.

Conflict of Interest
None declared.

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