SMARCB1 (INI-1)-deficient Sinonasal Carcinoma: A Case Report and its Clinical Implications on Diagnosis and Management

Dianne Mae Tan,[1] Glezette Anne Altares,[1] Rose Lou Marie Agbay,[1] Jose Carnate Jr.[1,2]

[1]*Department of Laboratory Medicine and Pathology, The Medical City, Pasig City, Philippines*
[2]*Department of Pathology, College of Medicine, University of the Philippines Manila*

ABSTRACT

SMARCB1 (INI-1)-deficient sinonasal carcinoma is a rare, poorly differentiated, and locally aggressive neoplasm. Frequently, this disease entity mimics benign head and neck diseases hence it poses a challenge to diagnose and manage such cases. Herein, we have documented a case of a 66-year-old female who presented with a right nasal mass on endoscopy. On microscopy, well-defined nests of plasmacytoid tumor cells infiltrating a desmoplastic stroma with areas of necrosis with focal hemorrhages were noted. Based on the histomorphology and immunohistochemistry studies, this case was signed out as SMARCB1 (INI-1)-deficient (sinonasal) carcinoma. This is the first reported case in the Philippines based on a search of local journal databases. Recent advancements in therapeutics point out the value of providing molecular characterization of these tumors.

Key words: SMARCB1-deficient Tumors, SMARCB1 (INI-1) gene, sinonasal carcinoma, poorly differentiated sinonasal carcinoma, undifferentiated sinonasal carcinoma

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Corresponding author: Dianne Mae B. Tan, MD, MBA
E-mail: diannemaetan@gmail.com
ORCiD: https://orcid.org/0009-0008-3474-9171

INTRODUCTION

SMARCB1 (INI-1)-deficient sinonasal carcinoma is a rare, poorly differentiated, and locally aggressive neoplasm. It is often diagnosed at an advanced stage, as it initially mimics benign conditions like epistaxis, allergic rhinitis, sinusitis, or presence of nasal polyps. In advanced stages, it can invade the orbits or cranium, causing ophthalmologic and neurologic symptoms, distant metastases, and eventual death.[1] With the advent of immunohistochemistry and molecular studies, morphologically poorly differentiated sinonasal carcinomas can now be classified further, providing insights on their diagnosis, prognosis and management with the use of novel therapeutic agents.[2]

Currently, there are no reported cases published in the Philippines (HERDIN and Philippine E-Journal). Hence, it is important to document the findings of a SMARCB1 (INI-1)-deficient sinonasal carcinoma and describe its key histomorphologic and immunohistochemistry findings.

CASE

The patient is a 66-year-old female, non-smoker and a former factory worker, with a one-month history of a right nasal cavity mass accompanied by congestion, facial pain, rhinorrhea, proptosis, and diplopia. The CT scan showed a large hyperdense mass arising from the right ethmoid sinus and invading the right maxillary sinus and sphenoid sinus with extension towards the right orbit (Figure 1). The initial impression was that of an esthesioneuroblastoma and a biopsy was subsequently performed.

Gross examination showed multiple cream-tan to dark brown irregularly shaped soft tissues measuring from 0.4 up to 1.3 cm in widest diameter with a soft tan-brown cut surface. Microsections show irregular nests of plasmacytoid tumor cells infiltrating a desmoplastic stroma with areas

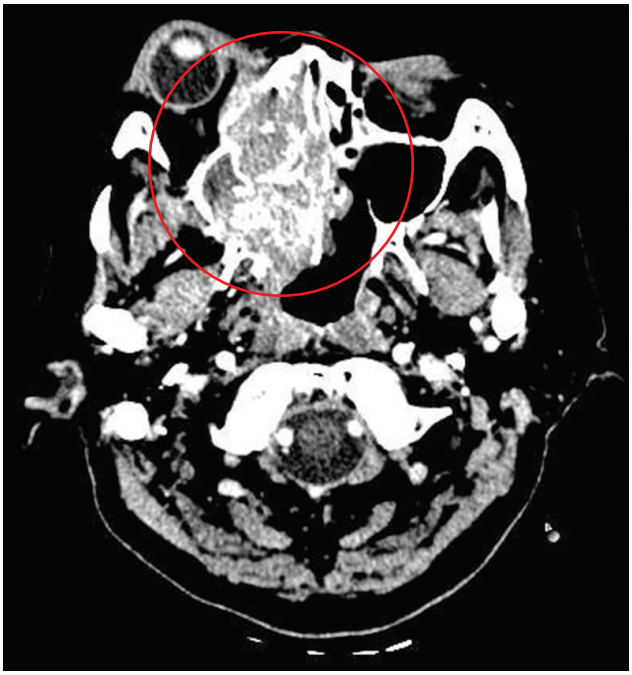

Figure 1. Head CT scan (axial view, brain window) shows a large hyperdense mass *(red circle)* arising from the right ethmoid sinus, invading the right maxillary sinus and sphenoid sinus, and extending to the right orbit.

of necrosis and hemorrhage. The tumor cells exhibit eccentric, ovoid, and hyperchromatic nuclei, some with prominent nucleoli, and ample eosinophilic cytoplasm. No gland formation was observed (Figures 2 and 3).

The case was initially signed out as a round cell neoplasm. Immunohistochemistry studies showed tumor cells that were positive for EMA, pancytokeratin, p63, and p40, and negative for synaptophysin, chromogranin, CD56, S100, desmin, SMA, and PR. INI-1 showed complete loss of nuclear expression in the cells of interest (Figure 4).

Given the morphologic and immunohistochemical profile of the mass, this case was signed out as SMARCB1 (INI-1)-deficient (sinonasal) carcinoma.

DISCUSSION

The SWI/SNF family of chromatin remodeling complexes are key regulators of nucleosome positioning and are composed of large, complicated macromolecules with various subunits attached. Their nomenclature, established by the Human Genome Organization, remains problematic due to the presence of multiple synonymous terms.[3] SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1), also known as integrase interactor 1 (INI-1), is a tumor suppressor gene found at chromosome 22q11.2 which encodes a protein subunit of SWI/SNF nucleosome remodeling complex. SMARCB1 is normally expressed in all cells.[4,5]

The loss of nuclear expression of the *SMARCB1* gene is often caused by biallelic inactivation through homozygous deletion, intragenic deletions, frameshift or nonsense mutations, or chromosomal loss (monosomy 22). It is central to the pathogenesis of various pediatric and adult sarcomas which include atypical teratoid rhabdoid tumors of the central nervous system, malignant rhabdoid tumors of the kidney and soft tissue, and SMARCB1 (INI-1)-deficient sinonasal carcinoma to name a few entities.[6] Interestingly, these tumors are reported to be genomically stable with the SMARCB1 gene being the only one altered. This is a finding that contrasts with the genetic instability that is a hallmark of most cancers.[7] Currently, it is still unknown how SMARCB1-deficient cancers arise in adults. In recent studies, rhabdoid tumors arise from the neural crest cells that lose SMARCB1 during development suggesting that SMARCB1-deficient tumors are often seen more in children than in adults.[8]

Histomorphologically, several studies have reported that the most common presentation of this neoplasm is an undifferentiated basaloid or "blue cell" tumor forming solid well-demarcated nests and sheets infiltrating a desmoplastic stroma. In the basaloid variant, the tumor cells have occasional palisading of the nucleus and high nucleus:cytoplasm ratios. Occasional singly scattered rhabdoid or plasmacytoid cells can also be identified. Squamous differentiation is not appreciated in all reported cases of this type. The second most common type would

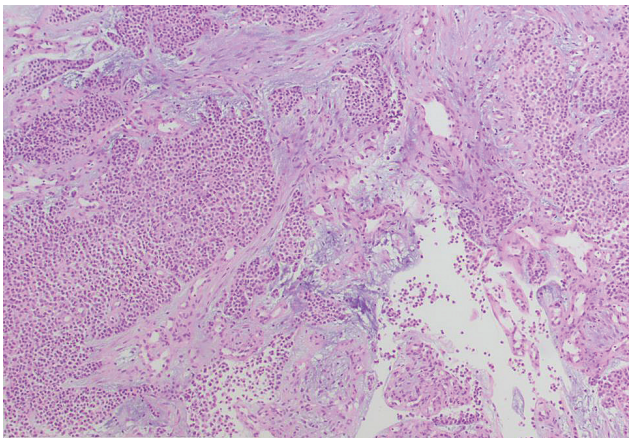

Figure 2. Biopsy of the mass shows irregular nests and sheets of plasmacytoid tumor cells infiltrating the stroma (H&E, 100x).

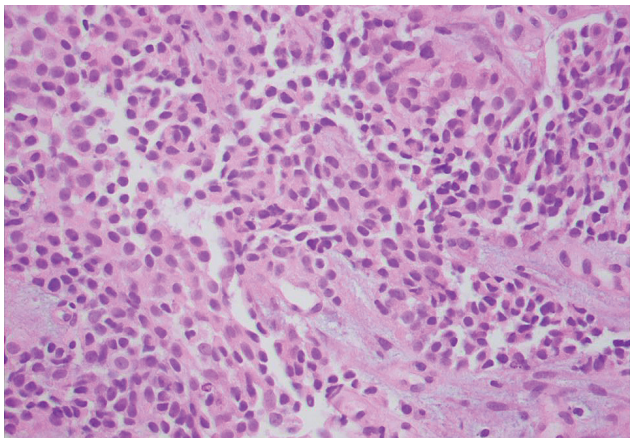

Figure 3. The biopsy shows tumor cells with eccentric, ovoid and hyperchromatic nuclei, some with prominent nucleoli, and ample eosinophilic cytoplasm (H&E, 400x).

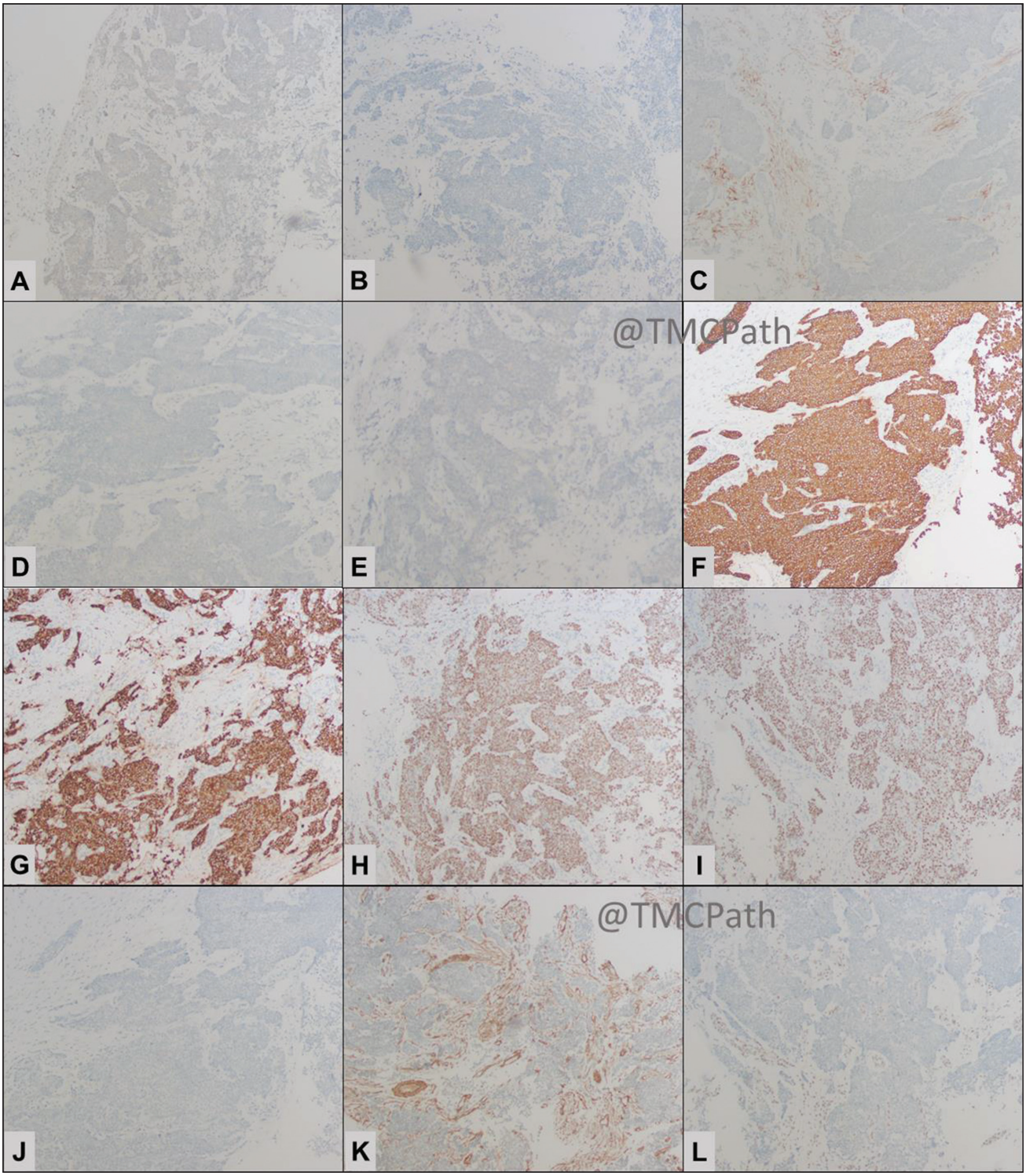

Figure 4. The immunohistochemistry panel of the biopsied mass (Immunohistochemistry stain, horseradish peroxidase method, 100x). The tumor cells stained negative for S100 **(A)**, desmin **(B)**, CD56 **(C)**, synaptophysin **(D)**, chromogranin **(E)**, PR **(J)**, and SMA **(K)** while stained positive for pancytokeratin **(F)**, EMA **(G)**, p63 **(H)**, and p40 **(I)**. INI-1 **(L)** exhibits loss of nuclear expression in the cells of interest).

be the plasmacytoid/rhabdoid or "pink cell tumor" variant which is described as nests and sheets of predominantly plasmacytoid cells. The tumor cells exhibit large oncocytic squamoid cells with acantholytic-like arrangement similar to oncocytic adenocarcinoma of the salivary glands. Other histomorphological features have been described in other reported cases such as pure sarcomatoid carcinoma types, plasmacytoid tumors with glandular differentiation, and mixed types.[9,10] In this case, the biopsied mass exhibited irregular nests of numerous tumor cells that are plasmacytoid in morphology.

Distinguishing between various poorly differentiated sinonasal carcinomas through morphology alone is difficult hence, immunohistochemistry stains are often requested. Common histomorphologic differentials for SMARCB1-deficient sinonasal carcinoma include basaloid squamous cell carcinoma, neuroendocrine tumors, and NUT carcinoma. Squamous cell carcinomas would typically express cytokeratins such as CK5/6 and pancytokeratins, while neuroendocrine tumors would stain positive for chromogranin, synaptophysin, and CD56 but lack cytokeratin expression. NUT carcinomas are distinctly positive for NUT protein. SMARCB1-deficient tumors may show variable expression of squamous markers and neuroendocrine markers but are negative for NUT protein. The most definitive immunohistochemical finding of this type of tumor is the loss of SMARCB1 (INI-1) expression in tumor cells, a feature typically retained in other sinonasal malignancies.[9,10] As mentioned previously, the loss of INI-1 is the hallmark of many rare and aggressive teratoid/rhabdoid tumors. The INI-1 immunohistochemistry stain has a high specificity and sensitivity in these types of tumors including SMARCB1-deficient sinonasal carcinomas. In most cases, immunohistochemistry is sufficient for diagnosis, and molecular testing is not clinically indicated, except in difficult or complex cases where loss of SMARCB1 expression cannot be confirmed.[10,11]

SMARCB1-deficient carcinomas are associated with a high recurrence rate and a worse prognosis compared to the other types of poorly differentiated sinonasal carcinomas with patients dying of the disease from zero to two (0-2) years from diagnosis.[12] Aggressive treatment, with surgical resection followed by adjuvant radiotherapy and concurrent chemotherapy, is often indicated.[13] With the advent of immunotherapy and targeted treatment, one promising target being studied is the enhancer-of-zeste-homolog-2 (EZH2) enzyme. Under normal conditions, SMARCB1 within the SWI/SNF complex suppresses PRC2–EZH2 activity, leading to the activation of tumor suppressor genes and repression of cell cycle–promoting genes. In contrast, the loss of SMARCB1 enhances PRC2–EZH2 activity. EZH2 inhibitors, such as tazemetostat, target the PRC-EZH2 complex hence preventing the upregulation of the oncogenic pathways such as *myc*, *sonic hedgehog*, and *WNT-β-catenin* similar to how SMARCB1 functions. Phase I and Phase II clinical trials for tazemetostat are reported to be ongoing.[14] In a case study done by Zhao and colleagues, PDL-1 inhibitors such as pembrolizumab were incorporated in the treatment regimen of three patients with SMARCB1-deficient sinonasal tumors. Two patients achieved a complete response, while the third, despite experiencing recurrence following treatment interruption, demonstrated sustained disease control with PDL-1 inhibition in later stages. This implies that PDL1 inhibitors may improve clinical outcomes of these patients.[15] Other targeted therapies such as histone deacetylase inhibitors, aurora-A-kinase inhibitors, and CDK4 inhibitors are being investigated in other carcinomas and sarcomas with SMARCB1-deficiency.[16] Recent discoveries and advancements in therapeutics point out the value of providing molecular characterization of these aggressive tumors.

CONCLUSION

The case presented in this paper highlights the importance of recognizing SMARCB1 (INI-1)-deficient sinonasal carcinoma as among the differential diagnosis of a poorly differentiated sinonasal carcinoma, the challenges in clinically diagnosing the entity, and its histomorphologic and immunohistochemistry findings. Advancements in the molecular characterization of these aggressive carcinomas may provide key insights on their pathogenesis, diagnosis, and optimal management. Awareness and early recognition of the entity may help positively impact the overall survival of affected patients.

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ETHICAL CONSIDERATION

Despite multiple efforts to obtain informed consent, the patient could not be reached. Due diligence was exercised in attempting to locate the family (absence of a recorded address, lack of responses, and no available cellphone or landline as verified by the Records Section), and the patient was ultimately lost to follow-up.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

DATA AVAILABILITY STATEMENT

No datasets were generated or analyzed for this study.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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