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INI 1 Retained Sinonasal Undifferentiated Carcinoma Masquering as Alveolar Rhabdomyosarcoma -A Rare Case Series

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ABSTRACT

Background: Sinonasal Undifferentiated carcinoma (SNUC) is a rare, aggressive malignancy of the sinonasal tract. Its clinical and histopathological presentation can often mimic other malignant tumors, including alveolar rhabdomyosarcoma (ARMS), which is characterized by small round cells and rhabdoid morphology. Distinguishing between these entities is crucial for appropriate treatment and prognosis. This case series highlights instances where SNUC was initially misdiagnosed as alveolar rhabdomyosarcoma due to overlapping morphological features but was ultimately identified through immunohistochemical (IHC) analysis, particularly with the retention of INI1 expression.

Case Presentation: We present a series of three cases with sinonasal tumors initially presented with symptoms such as epistaxis, nasal obstruction, and facial pain. Imaging studies revealed masses involving the maxillary sinuses and nasal cavities, suggestive of aggressive sinonasal tumors. Initial biopsies showed small round cells arranged in sheets and nests, with some cells exhibiting rhabdoid morphology, leading to a preliminary diagnosis of high-grade undifferentiated tumors, including alveolar rhabdomyosarcoma. However, further immunohistochemical analysis, including markers such as EMA, pancytokeratin (AE1/AE3), and INI1, revealed retained INI1 expression, which is characteristic of sinonasal undifferentiated carcinoma. The diagnosis of SNUC was confirmed, and treatment plans were adjusted accordingly.

Results: All three cases demonstrated INI1 retention, which helped distinguish SNUC from other differential diagnoses, such as alveolar rhabdomyosarcoma and sinonasal undifferentiated tumors. Immunohistochemistry proved essential in guiding accurate diagnosis, particularly in differentiating SNUC from mimicking malignancies. The Ki-67 index was notably high in all cases, reflecting the aggressive nature of the tumors.

Conclusion: This rare case series underscores the importance of a comprehensive diagnostic approach, including immunohistochemistry, in differentiating sinonasal undifferentiated carcinoma from other malignancies like alveolar rhabdomyosarcoma. Retention of INI1 expression is a key marker for diagnosing SNUC, even when it presents with histological features that overlap with more common sinonasal malignancies. Timely and accurate diagnosis is critical for appropriate management and prognosis.

Keywords: *Alveolar rhabdomyosarcoma, Sinonasal, Carcinoma*

1. INTRODUCTION

Sinonasal Undifferentiated Carcinoma (SNUC) is a rare, aggressive malignancy that arises in the sinonasal region, typically presenting with nonspecific symptoms such as nasal obstruction, epistaxis, and facial pain[1]. Despite its rarity, SNUC has an important clinical significance due to its aggressive nature and poor prognosis. This carcinoma is known for its histopathological diversity, which can often complicate diagnosis, especially when it presents with features resembling other

malignancies.[2] One such condition is Alveolar Rhabdomyosarcoma (ARMS**)**, a type of soft tissue sarcoma that often occurs in the head and neck region in pediatric patients.

In the rare occurrence of an INI 1-retained SNUC, the carcinoma may exhibit histological features that closely resemble those of ARMS. The INI 1 protein (also known as SMARCB1) plays a crucial role in chromatin remodeling and is a critical tumor suppressor in various cancers.[3] The loss of INI 1 expression has been widely recognized as a characteristic feature of certain malignancies, such as rhabdoid tumors. However, the retention of INI 1 expression in SNUC, particularly when it mimics ARMS, can pose a significant diagnostic challenge.[4]

This phenomenon of INI 1-retained SNUC masquerading as ARMS necessitates a high level of clinical awareness and a multi-disciplinary diagnostic approach, including immunohistochemical staining, molecular studies, and radiographic imaging, to ensure accurate diagnosis and appropriate management.[4,5] Understanding the unique features of this entity is crucial for pathologists and oncologists, as misdiagnosis can lead to suboptimal treatment strategies and poorer patient outcomes.

In this context, the identification of an INI 1-retained SNUC that presents with clinical and histopathological features of ARMS emphasizes the importance of distinguishing between these two entities, given their distinct biological behaviors, prognostic implications, and treatment approaches.

In this report we present three rare cases of undifferentiated tumors resembling small round cell tumors and immunohistochemically confirmed as SNUC.

Case 1:

A 62-year-old patient presented to a tertiary care center with a one-month history of left-sided hyposmia, nasal blockage, and epistaxis, along with two months of left eye redness and headache. The patient had a past medical history of COPD. Clinical examination revealed a pale reddish mass, a deviated nasal septum (DNS) with synechiae on the left side, along with a reddened left eye and congested conjunctiva. CT of the paranasal sinuses (PNS) showed complete fullness in the left maxillary sinus, bony erosion of the hard palate and medial orbital wall, and complete obliteration of the left nasal cavity, suggestive of a suspected growth with bony wall erosion. The patient underwent diagnostic nasal endoscopy (DNE) with biopsy. The gross specimen consisted of a single tissue fragment measuring 3x0.5x0.5 cm (A/E). Histopathological examination revealed fragments of tissue lined by respiratory epithelium, with a malignant neoplasm arranged in lobules composed of round to oval cells with scant cytoplasm and hyperchromatic nuclei. Some rosette-like structures were also observed. The differential diagnosis was given as:

1. **Olfactory neuroblastoma**
2. **Alveolar rhabdomyosarcoma**

Immunohistochemical (IHC) studies were advised for further diagnosis. A panel of markers, including EMA, Ki-67, S100, CK7, synaptophysin, chromogranin A, desmin, and myogenin, was employed. Only EMA showed positivity, with a Ki-67 index of 4%. To exclude the diagnosis of sinonasal undifferentiated carcinoma, an additional IHC panel including AE1/AE3, Vimentin, WT1 (C-terminal), MyoD1, and SMA was performed. AE1/AE3 showed positive expression, further supporting the diagnosis of sinonasal undifferentiated carcinoma. To confirm the diagnosis and exclude desmoplastic small round cell tumor, an IHC panel including CD56, NSE, CAM 6.2, and IDH2R172 was performed. The results showed negative expression for these markers, while INI1 staining was retained, which supports the diagnosis of sinonasal undifferentiated carcinoma.

Case2:

A 45-year-old female patient presented with a 7-month history of epistaxis and nasal obstruction. X-ray revealed a mass in the left maxillary antrum extending into the nasal cavity. Biopsy showed small round cells arranged in sheets and nests, with some cells exhibiting rhabdoid morphology. The initial impression was a high-grade undifferentiated tumor, suggesting alveolar rhabdomyosarcoma. Immunohistochemistry was performed, showing positivity for desmin, pancytokeratin (AE1/AE3), CK7, and EMA, with retained INI1 expression, supporting the diagnosis of sinonasal undifferentiated tumor.

Case3:

A 60-year-old patient presented with epistaxis for 3 months, along with left eye redness and headache for 11 months. Clinical examination revealed a pale reddish mass and a deviated nasal septum (DNS). CT scan showed a mass in the maxillary sinus extending into the nasal cavity, causing complete obliteration of the left nasal cavity. The patient underwent biopsy, and the gross specimen consisted of multiple fragile tissue fragments measuring 0.5x0.5 cm (A/E). Histopathology revealed fragments of tissue with cells showing rhabdoid morphology. The impression was a high-grade undifferentiated tumor, and immunohistochemistry markers were suggested. The immunohistochemical panel showed positivity for EMA, pancytokeratin (PanCK), and retained INI1 expression. Ki-67 index showed 40% high positivity. The morphological

diagnosis was malignant round cell tumor

Target population	Tumor cells
Positive markers	Pan CK
Negative markers	Vimentin,WT1,MyoD1,SMA,Myogenin,Synaptophysin

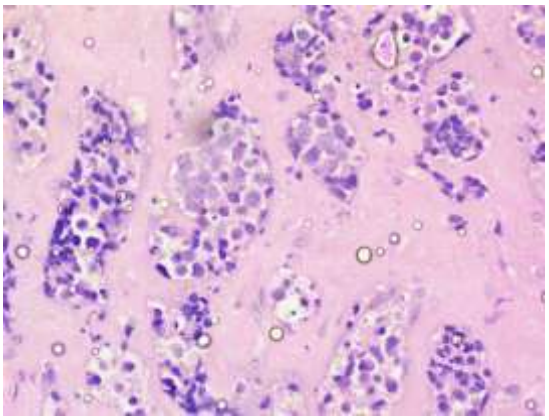


Figure1:H&E(High Power)

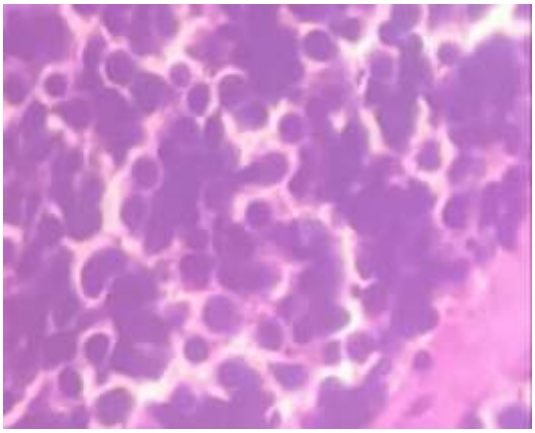


Figure2 :H&E(HighPower)

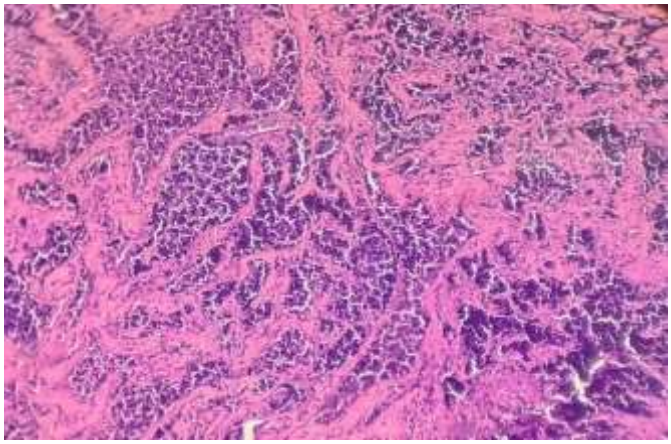


Figure 3:H&E (Low Power)

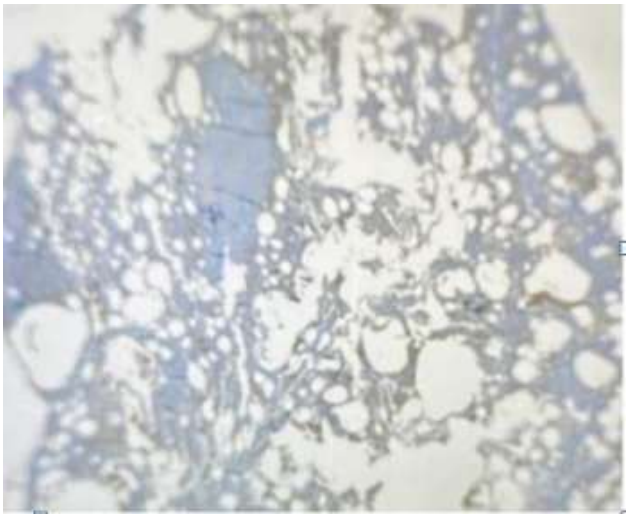


Figure4: INI1 retained

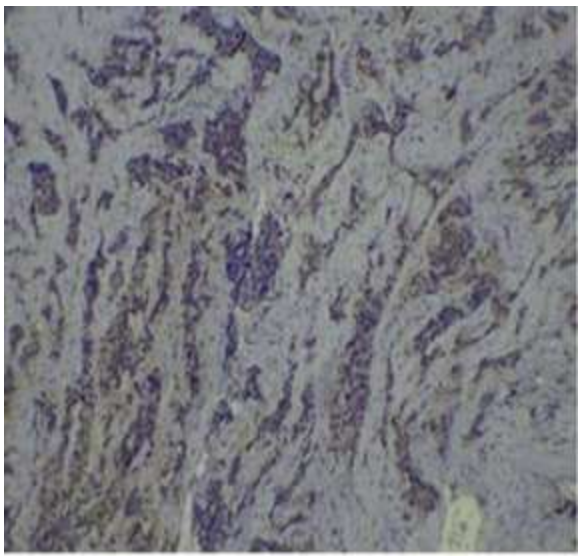
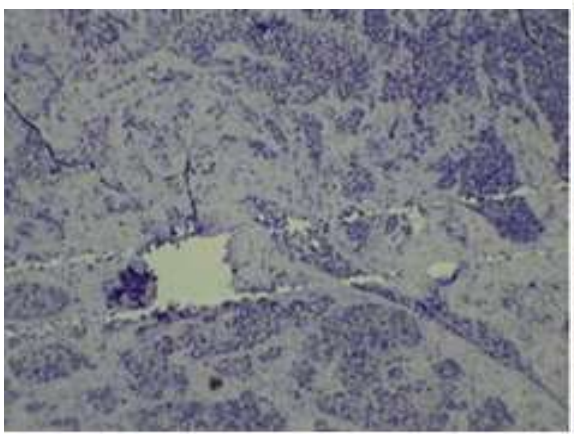


Figure5: EMA positive



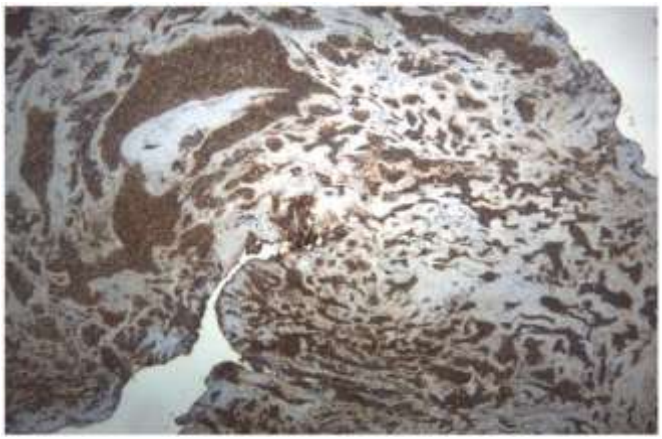


Figure 6 : Ki67 (4%) **Figure7: Pan CK Positive**

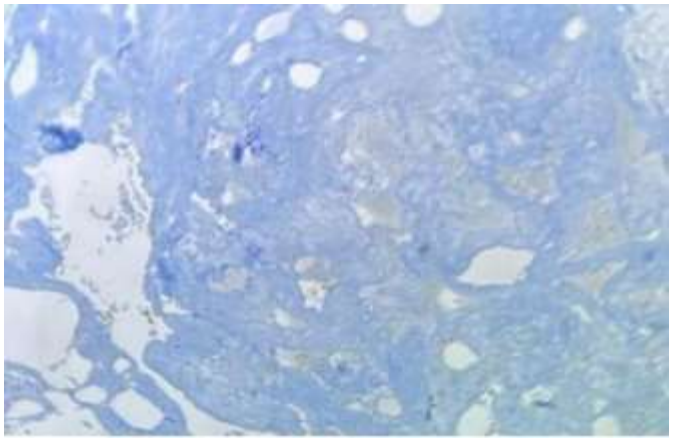


Figure 8: CAM 5.2 Negative

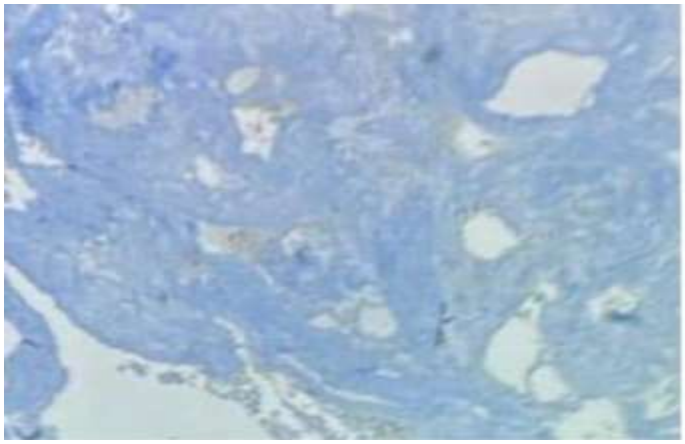


Figure 9: CD56 Negative

2. DISCUSSION

Sinonasal Undifferentiated Carcinoma (SNUC) is a rare and aggressive neoplasm that originates in the sinonasal mucosa. These tumors are typically large (>4 cm) at the time of initial clinical presentation and are characterized by features such as ulceration, bone destruction, lymphovascular invasion, perineural invasion, and extensive necrosis. The tumor cells of SNUC are arranged in sheets, lobules, and trabeculae, consisting of atypical but monotonous polygonal cells with round to irregular nuclei, well-defined cell borders, and ample cytoplasm. The nuclear chromatin appears vesicular to open, with prominent nucleoli.[6] Neuroendocrine morphologic features are notably absent, but apoptosis and increased mitosis are commonly identified. Additionally, rosettes may be present, especially in cases exhibiting more basaloid growth or rhabdoid features.

A significant feature in the diagnosis of SNUC is the loss of SMARCB1 (INI-1) protein expression, typically through immunohistochemistry. The absence of INI1 may suggest a different tumor type, but SNUC can still present with retained SMARCB1 expression, complicating the differential diagnosis with other malignancies like alveolar rhabdomyosarcoma (ARMS).[7,8] Despite advances in molecular biology, the prognosis of SNUC remains poor, with overall survival rates exceeding 50% at five years.

The increasing availability of specific and sensitive immunohistochemical antibodies, as well as novel genetic tools, has led to the identification of genetically defined subtypes within the broader category of SNUC. This includes entities such as NUTM1 rearranged carcinomas (NUT) and carcinomas associated with inactivation of components of the SWI/SNF chromatin remodeling complex (e.g., SMARCB1-deficient and SMARCA4-deficient carcinomas). Recent studies have also highlighted the frequent presence of oncogenic IDH2 mutations in the vast majority of SNUC cases, marking it as a distinctive neoplastic disease with unique molecular characteristics.[9,10,11]

While SNUC is a rare malignancy, its late presentation and complex anatomic location make it one of the most challenging cancers in the head and neck region. The tumor's rarity, combined with its lack of specific histologic features, makes the diagnosis particularly difficult. Advances in molecular techniques, surgical approaches, chemotherapy, and radiation protocols have contributed to incremental improvements in survival rates over the years.[12,13] However, despite these

advancements, the overall prognosis remains guarded, especially considering the lack of glandular or squamous differentiation in these tumors.

Immunohistochemical staining for epithelial markers such as AE1/AE3, CK7, OSCAR, CAM 5.2, EMA, P16, and CD117 is typically diffuse and strong in SNUC. However, these tumors do not stain positive for markers like CK5/6, p40, CEA, EBER, CD34, desmin, S100, calretinin, or SMARCB1 in cases of SNUC that are SMARCB1-deficient. The loss of INI1 expression, a key feature of SMARCB1-deficient SNUC, has been recognized as a distinct genetic alteration within the tumor's molecular landscape.

SMARCB1-deficient SNUC has been identified as a specific entity within the broader category of sinonasal malignancies. To date, approximately 70 cases have been reported. These tumors generally develop in middle-aged individuals (ranging from 19 to 89 years), with a slight male predilection. SMARCB1-deficient SNUC often presents with undifferentiated basaloid morphology and may feature rhabdoid or plasmacytoid cytology.[14] In contrast, SMARCA4-deficient SNUC, which retains SMARCB1 expression, has also been identified but is much rarer, with only two cases reported.

The prognosis for SNUC remains poor, with a 5-year overall survival rate generally exceeding 50%. Sinonasal malignancies, including SNUC, are rare, occurring at an incidence of 0.5–2.6 per 100,000 people per year, and represent less than 1% of all cancers. SNUC tends to affect males more frequently (a male-to-female ratio of 2.1:1), and it can occur across a wide age range, from 20 to 90 years old.

Alveolar Rhabdomyosarcoma (ARMS), on the other hand, is a rare malignant tumor with characteristic plasmacytoid rhabdoid features. This tumor often exhibits a sheet-like or alveolar pattern of round to spindle-shaped rhabdomyoblasts, with pleomorphism, variable mitotic activity, limited necrosis, and rare lymphovascular invasion. Unlike SNUC, ARMS expresses markers like CD56, AE1/AE3, and EMA (10% expression), along with synaptophysin (30%) and chromogranin (20%). It is crucial to differentiate ARMS from SNUC, especially in head and neck regions, where both conditions can present similarly as small, blue cell tumors.

Diagnosis of small round cell tumors is challenging, particularly in the head and neck, where differential diagnoses like small cell carcinoma, olfactory neuroblastoma, and malignant melanoma are common. The difficulty in diagnosis is compounded by the fact that ARMS variants, particularly alveolar and solid types, can mimic other small round blue cell tumors, such as small cell carcinoma, lymphoma, neuroblastoma, and malignant melanoma. Thus, immunohistochemical analysis plays a crucial role in distinguishing ARMS from other malignancies, and aberrant immunoreactivity may further complicate the diagnosis.

A study by Amrita Bahrami et al. found that 50% of ARMS cases exhibited positivity for epithelial markers, with 32% expressing **s**ynaptophysin and 22% expressing chromogranin. In contrast, a study by Houreih MA et al. described three cases of ARMS, one involving the orbit of a 20-year-old male, in which all three tumors tested positive for desmin, myogenin, and synaptophysin, with two cases showing positivity for chromogranin.[15]

Ultimately, accurate diagnosis and differentiation of SNUC from ARMS and other small round blue cell tumors are paramount in guiding treatment strategies and improving patient outcomes. The combination of clinical, histopathological, and molecular tools is essential in managing these complex cases effectively.

Comparison:

Sinonasal undifferentiated carcinoma	Ewings/PNET	OlfactoryNeuroblastoma
Morphology		
PatternSheets,nests Tumor invade as sheets of monotonous Undifferentiated cells, frequently showing bone invasion and tumor necrosis, moderate cytoplasm, vericular chromatin, vesicular chromatin, small nucleoli,	Round cells are patchy/ lobular and fibrovascular septa are observed between lobuleswithvaryingwidthof fibrous connective tissue. Cytoplasm of tumor cells is scarce and unclear. Thenuclei are round/oval, dark stained/uniform and mitosis	Round cells are nested and trabeculatedThe interlobular spaces are vascular rich and contain fibrous connective tissue.

foci of keratinization,		
Positiveexpression	Positiveexpression	Positiveexpression
Pan CK (AE1/AE3),CK7(40%)	OFCD99,Vimetin,cyclinD, expression of neuroendocrine. marker, no expression of epithelial marker WT1, Desmin, S100, NF	Neuroendocrine. marker (such as NSE, Synaptophysin) NF,GFAP,S100epithelial marker,noexpressionof dermin,EMA,CD99
EMA(30%)		
LAM5.2(50%)		
Synaptophysin(<15%)		
Chromogranin(<1.5%)		

3. CONCLUSION

In diagnosing small round blue cell tumor morphological evaluation alone is not sufficient. Immunohistochemical study is mandatory and evaluation of right panel of markers are important for prognostic and therapeutic implications. Cytogenetic and molecular testing is important in management and prognosis.

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