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Original contribution

Sinonasal undifferentiated carcinoma: clinicopathological spectrums and diagnosis reappraisal☆,☆☆

Elmira Vaziri Fard MD[a], Songlin Zhang MD, PhD[a], Zhenjian Cai MD, PhD[a], Jianmin Ding PhD[a], Qigang Sun MD[a,b], Karan Saluja MD[a], Hui Zhu MD PhD[a,*]

[a]*Department of Pathology and Laboratory Medicine, University of Texas Health Science Center at Houston, Houston, TX 77030, USA*
[b]*Department of Hepatobiliary Surgery, Hainan General Hospital, Hainan 570311, China*

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Summary Sinonasal undifferentiated carcinoma (SNUC) is defined as undifferentiated carcinoma of the sinonasal tract without glandular or squamous features and not otherwise classifiable. SNUC is a rare tumor, with a long list of differential diagnoses, and often poses a considerable diagnostic challenge. In addition, recent advances in molecular and immunohistochemistry techniques have recognized several new entities that were previously included in the SNUC category. These include SMARCB1 (INI-1)–deficient carcinoma, NUT (nuclear protein in testis) carcinoma, adamantinoma-like Ewing sarcoma, and the most recently described and rarer SMARCA4 (BRG)–deficient carcinoma. In this study, we retrospectively reviewed 11 cases with an original diagnosis of SNUC. We found that a significant portion of those cases can be reclassified into specific entities, with potential impact on therapy and prognosis because of misclassification in 2 of these cases.
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1. Introduction

Sinonasal tract is a small anatomic region that can give rise to a tremendous variety of benign and malignant neoplasms [1]. Malignant sinonasal tract tumors are rare, accounting for less than 1% of all neoplasms and 5% of head and neck neoplasms [2,3]. Approximately 50% of malignant sinonasal tumors are squamous cell carcinomas. The remaining 50% comprise more than 30 different neoplastic entities, many of which are very rare, placing familiarity out of reach for many practicing pathologists [3]. Sinonasal undifferentiated carcinoma (SNUC) is one of those rare sinonasal malignant neoplasms.

In the current *World Health Organization Classification of Head and Neck Tumors*, SNUC is defined as an undifferentiated carcinoma of the sinonasal tract without glandular and squamous features and not otherwise classifiable [1]. It is considered a diagnosis of exclusion and represents a

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* Corresponding author at: 6431 Fannin St, MSB 2.290, Houston, TX 77030.
E-mail address: hui.zhu@uth.tmc.edu (H. Zhu).

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heterogeneous group of tumors. Morphologically, SNUC is typically a high-grade blue cell tumor with necrosis, and brisk mitotic and apoptotic activity. Immunohistochemically, SNUC is positive only for pancytokeratin (AE1/AE3) and simple keratins such as CK7, CK8, and CK18. At the molecular level, *SOX2* amplification and *IDH2* mutations were detected in a subset of SNUC [4,5].

The incidence of SNUC in the United States is 0.2 per million, with a male-to-female ratio of 2:1 to 3:1. Age ranges widely from 8 to 85 years at the time of diagnosis, with a mean age of 57.8 years [6,7]. Clinically, patients usually present with locally aggressive tumor with frequent involvement of the orbit and skull base [1,6]. Given its aggressive behavior, multimodal therapies including combined surgery, chemotherapy, and radiotherapy are necessary for disease management of SNUC [1,8]. However, outcomes for the patients are poor with a median survival of 22 months and a 5-year survival rate of 34.9% [1].

Recent advances in molecular and immunohistochemistry techniques have identified distinct entities that were previously included in the SNUC category. These entities include NUT carcinoma [9], adamantinoma-like Ewing sarcoma [10], SMARCB1 (INI-1)–deficient sinonasal carcinoma [11], and SMARCA4 (BRG1)–deficient sinonasal carcinoma [12]. With the ever-growing advances in targeted therapy in the era of personalized medicine, an accurate diagnosis is important for identifying the appropriate treatment for individual patient. In this study, we retrospectively reviewed the clinicopathological presentations of 11 patients who were originally diagnosed as having SNUC. We found that a significant portion of those cases can be reclassified into specific entities, including large cell neuroendocrine carcinoma (LCNEC), SMARCB1-deficient sinonasal carcinoma, and Epstein-Barr virus (EBV)–associated nasopharyngeal LCNEC.

2. Materials and methods

This clinical investigation was conducted in accordance and compliance with guidelines of an institutional internal review board authorization (HSC-MS-16-0967). Eleven cases that were originally diagnosed as SNUC between January 2010 and May 2018 were retrieved from the routine surgical pathology files. Tumor specimens were fixed in 10% neutral-buffered formalin and embedded in paraffin for routine histologic examination. Patients' medical records and all slides from resection/biopsy, including hematoxylin and eosin (H&E) and immunohistochemically stained slides, were retrieved and reviewed. Additional immunohistochemical studies were performed on 4-μm sections cut from paraffin-embedded blocks using a fully automated system (Dako Omnis, Agilent, Santa Clara, CA) for the following antibodies: CD117 (dilution 1:800; Agilent, Santa Clara, CA), p16 (clone E6H4, ready to use antibody; Ventana, Tuscan AZ), INI-1 (dilution 1:200; BD Biosciences, San Jose, CA), INSM1 (clone A8, dilution 1:200; Santa Cruz Biotechnology, Santa Cruz, CA), NUT (clone C52B1, dilution 1:400; Cell Signaling, Dancer MA), ARID1A (dilution 1:200; Sigma Life Science, St.Louise, MO), and BRG1 (dilution 1:100; Abcam, Cambridge MA). For assessment of the staining results of SWI/SNF components (SMARCB1, SMARCA4, and ARID1A), the presence of strong nuclear staining in the background nonneoplastic cells is seen in all cases.

3. Results

Clinicopathological features of these 11 cases diagnosed as SNUC are shown in the Table. Patients' median age is 61 years (ranged from 19 to 75 years). There were 10 men and 1 woman. All patients except one (case 3) presented with large sinonasal tract destructive lesions with frequent erosion/invading into the orbit and skull base. Morphologically, most of these tumors (7/11) were blue cell tumors with high nuclear-to-cytoplasmic ratio. Four cases (4/11) had tumor cells with moderate amount of eosinophilic cytoplasm. Brisk mitotic and apoptotic activities were seen in all cases. Necrosis was present in most of these cases. The tumor cells formed sheets, trabeculae, nests, or single files with no obvious morphologic differentiation, with one case (case 2) showing diffuse rosette formation. Immunohistochemical stains were used in the initial workup for all cases, including AE1/AE3, CAM5.2, CK5/6, p63, CD99, desmin, myogenin, neuroendocrine markers, melanoma markers, and lymphoma markers. All cases were positive for AE1/AE3 and CAM5.2, and negative for squamous, melanoma, lymphoma, and skeletal muscle markers.

Case 1 was a sinonasal mass from a 19-year-old woman. The tumor cells had moderate amount of eosinophilic cytoplasm, prominent nucleoli, indistinct cell borders, and a predominantly nested growth pattern with peripheral palisading. Original workup showed that the tumor cells were positive for AE1/AE3, CAM5.2, CD56, chromogranin (focal), and neuron-specific enolase (NSE; focal) (Fig. 1), whereas synaptophysin was negative. Ki-67 labeling index was 70%. This case was originally diagnosed as SNUC with neuroendocrine differentiation. The patient was given combined chemoradiation after surgery and was disease-free after 7 years' of follow-up. Additional immunohistochemical stains showed that tumor cells were positive for INSM1 and p16 and negative for CD117. Given the presence of neuroendocrine morphology (nested growth pattern with peripheral palisading) and the positive staining for INSM1, CD56, and chromogranin, this case is reclassified as LCNEC.

Case 2 was a sinonasal mass from a 39-year-old man. Morphologically, this high-grade blue cell tumor showed extensive rosette formation (Fig. 2). Immunohistochemical studies showed that the tumor cells were diffusely positive

Table Clinicopathological presentations of 11 cases with original diagnosis of SNUC

Case	Age (y)	Sex	Clinical presentation	Treatment	Lymph node involvement	Clinical stage	INI-1	p16	CD117	INSM1	Diagnosis	Follow-up	Pathologic features
1	19	F	Large sinonasal mass with orbital and skull base involvement	Surgery, chemoradiation	No	IVB (T4bN0M0)	Retained	Pos	Neg	Pos	LCNEC	AOD 7 y	Tumor cells with moderate amount of cytoplasm, peripheral palisading, focal rosette formation, positive for CD56, INSM1, and chromogranin (focal)
2	39	M	Large sinonasal mass with orbital and skull base involvement	Surgery, chemoradiation	No	IVB (T4bN0M0)	Retained	Pos	Pos	Neg	SNUC	AWD 19 mo, with liver, lung, brain metastasis, discharged to hospice care	Blue cell tumor with extensive rosette formation, positive for cytokeratin; negative for p40, CD99, and neuroendocrine markers
3	69	M	Large nasophyngeal mass with neck lymph node metastasis	Surgery, chemoradiation	Level II lymph nodes	IVA (T3N2M0)	Retained	Neg	Neg	Focal	EBV-positive LCNEC of the nasopharynx	AOD 1 y, with complete clinical and radiologic response	Extensive lymphoplasmacytic infiltrate, EBER-ISH positive
4	61	M	Large sinonasal mass with orbital and brain extension, possible lung metastasis	Chemoradiation	Bilateral cervical lymph nodes	IVC (T4bN2M1)	Lost	Pos	Neg	Focal	SMARCB1-deficient sinonasal carcinoma	AWD 17 mo, with multiple bone metastasis	Tumor cells with moderate amount of eosinophilic cytoplasm, INI-1 loss
5	61	M	Large sinonasal mass with brain, liver and lung metastasis	Surgery, chemoradiation	No	IVC (T4bN0M1)	Lost	Neg	Neg	Neg	SMARCB1-deficient sinonasal carcinoma	AWD 11 mo, discharged to hospice care	Tumor cells with moderate amount of eosinophilic cytoplasm, INI-1 loss
6	75	M	Large sinonasal mass with bilateral orbital and skull base involvement	Chemoradiation	No	IVA (T4aN0M0)	Lost	Pos	Neg	Focal	SMARCB1-deficient sinonasal carcinoma	AWD 7 mo	Tumor cells with moderate amount of eosinophilic cytoplasm, INI-1 loss

7	76	M	Large sinonasal mass with skull base involvement and possible orbital involvement	Unknown (moved out of state)	No	IVA (T4aN0M0)	Retained	Pos	Pos	Focal	SNUC	No follow-up	High-grade blue cell tumor
8	64	M	Large sinonasal mass with intracranial extension	Surgery and chemotherapy	No	IVB (T4bN0M0)	Retained	Neg	Pos	Neg	SNUC	AWD 8 mo, suspicious for recurrence	High-grade blue cell tumor
9	67	M	Large sinonasal mass with intracranial extension and bilateral orbital involvement	Hospice care (no treatment)	No	IVB (T4bN0M0)	Retained	Pos	Pos	Focal	SNUC	Discharged to hospice care	High-grade blue cell tumor
10	46	M	Large sinonasal mass with extensive brain involvement and bilateral orbital involvement	Unknown (lost follow-up after diagnosis)	Unknown	Unknown (T4bN? M?)	Retained	Pos	Pos	Focal	SNUC	No follow-up	High-grade blue cell tumor
11	67	M	Large sinonasal mass with erosion into skull base and involvement of bilateral orbit	Surgery	Level II nodes	IVA (T3N2M0)	Retained	Pos	Pos	Focal	SNUC	No follow-up	High-grade blue cell tumor

Abbreviations: AOD, alive without disease; AWD, alive with disease; F, female; ISH, in situ hybridization; M, male.

for AE1/AE3 and CAM5.2. Other tested markers including neuroendocrine markers, melanoma markers, and lymphoma markers were all negative. Given the presence of rosette formation, differential diagnosis included adamantinoma-like Ewing sarcoma [10]. Additional stains added in this study showed that the tumor cells were negative for CD99 and p40, which have been shown to be positive in all cases of adamantinoma-like Ewing sarcoma [10]. To confirm that these rosette structures were not poorly formed glands, additional stains were performed and the tumor cells were negative for CK7, CK20, TTF-1, NKX3.1, CDX2, GATA3, and PAX8. Thus, a diagnosis of adenocarcinoma, primary or metastatic, was unlikely. The tumor cells showed diffuse strong positivity for p16 and CD117, 2 markers that are usually positive in SNUC [1]. Because rosette formation does not exclude a diagnosis of SNUC, this case remains in the SNUC category.

Case 3 was previously reported [13].The tumor arose from nasopharynx rather than sinonasal cavity in a 69-year-old man. The most characteristic finding of this case was marked intratumoral and peritumoral lymphoplasmacytic infiltration. The tumor cells were positive for AE1/AE3, CAM5.2, CD56, and synaptophysin (focal) and were also positive for EBV-encoded small RNA (EBER) by in situ hybridization.

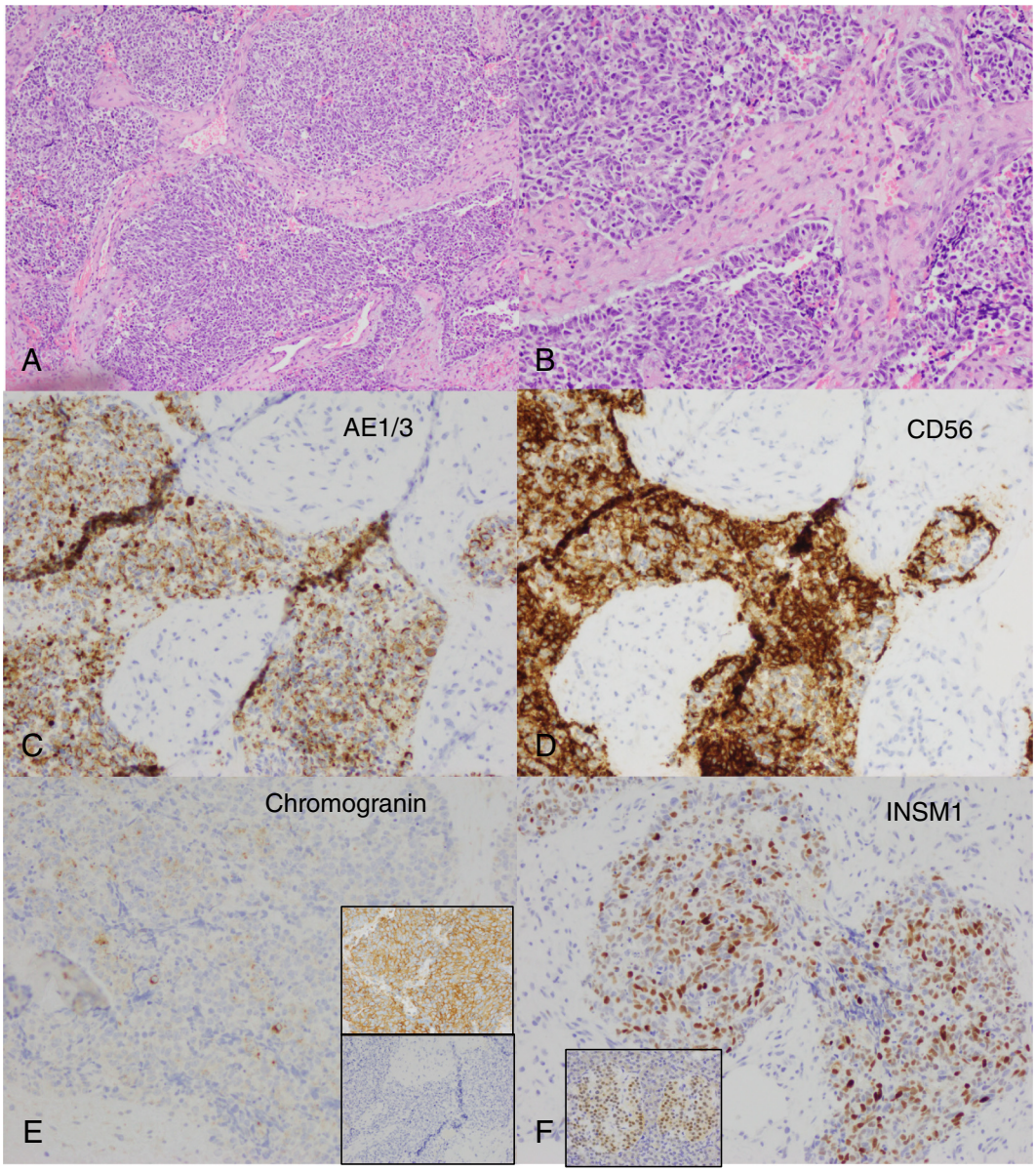

Fig. 1 LCNEC originally diagnosed as SNUC with neuroendocrine differentiation. A, Tumor cells with organoid/nested growth pattern (H&E, original magnification ×100). B, Tumor cells had prominent nucleoli with frequent mitotic figures and apoptotic bodies. Peripheral palisading and rare rosette formation were present (H&E, ×200). Tumor cells were positive for AE1/AE3 (C, ×100), CD56 (D, ×100), chromogranin (E, ×200; upper inset: chromogranin-positive control; lower inset: negative control [mouse] antibody), and INSM1 (F, ×200; inset: INSM1-positive control).

However, squamous markers including p63, p40, and CK5/6 were all negative. This was an extremely rare case and did not fit into any of the nasopharyngeal tumors included in the World Health Organization book. The lack of squamous differentiation ruled out the diagnosis of differentiated or undifferentiated nasopharyngeal carcinoma, which is squamous cell carcinoma arising from nasopharynx by definition and is diffusely positive for squamous markers [1]. Initially, the case was diagnosed as SNUC. However, the nasopharyngeal location and the association with EBV argue against an SNUC diagnosis. Upon further workup, the tumor cells were focally and weakly positive for INSM1 (Fig. 3), and negative for p16 and CD117. Cases with similar clinicopathological presentation and EBER positivity have been previously reported as EBV-positive LCNEC of the nasopharynx, and have been shown to respond well to combined radiation and chemotherapy [13-15].

Three cases (case 4, 5, and 6) showed loss of nuclear stain for SMARCB1. All 3 cases had tumor cells with moderate amount of eosinophilic cytoplasm with focal plasmacytoid/rhabdoid morphology, prominent nucleoli, and nested growth pattern (Fig. 4). These 3 cases are reclassified as SMARCB1-deficient sinonasal carcinoma [11].

SNUC can show very focal reactivity for chromogranin and synaptophysin [1] and therefore can be difficult to distinguish from high-grade neuroendocrine carcinoma (NEC). We examined the expression of a recently identified neuroendocrine marker, INSM1, in all 11 cases. Focal weak staining was seen in most of those cases (Fig. 4). Strong crisp nuclear staining was seen only in the sinonasal LCNEC case, but not in EBV-positive nasopharyngeal LCNEC. Negative staining (defined as <5% cells showing nuclear staining) was seen in 3 cases (Table).

Immunohistochemical stains for NUT, SMARCA4, and ARID1A were performed on all 11 cases to identify any potential NUT carcinoma or SMARCA4 (BRG1)–deficient sinonasal carcinoma. All 11 cases were negative for NUT staining and showed retained nuclear expression of SMARCA4 and ARID1A.

In summary, of the 11 cases, 3 are reclassified as SMARCB1-deficient carcinoma based on loss of SMARCB1 nuclear expression; 1 is reclassified as LCNEC based on positive staining of INSM1, CD56, and chromogranin; and 1 is reclassified as EBV-positive nasopharyngeal LCNEC based on the clinicopathological findings. The remaining 6 cases are kept in the SNUC category (Table).

CD117 and p16 have been shown to be positive in SNUC and can be helpful in establishing a diagnosis of SNUC in challenging cases [1]. In this study, we found that CD117 was positive in all 6 SNUC cases and negative in all 5 cases that were reclassified as non-SNUC. p16 was positive in 5 of 6 SNUC cases, and was also positive in sinonasal LCNEC

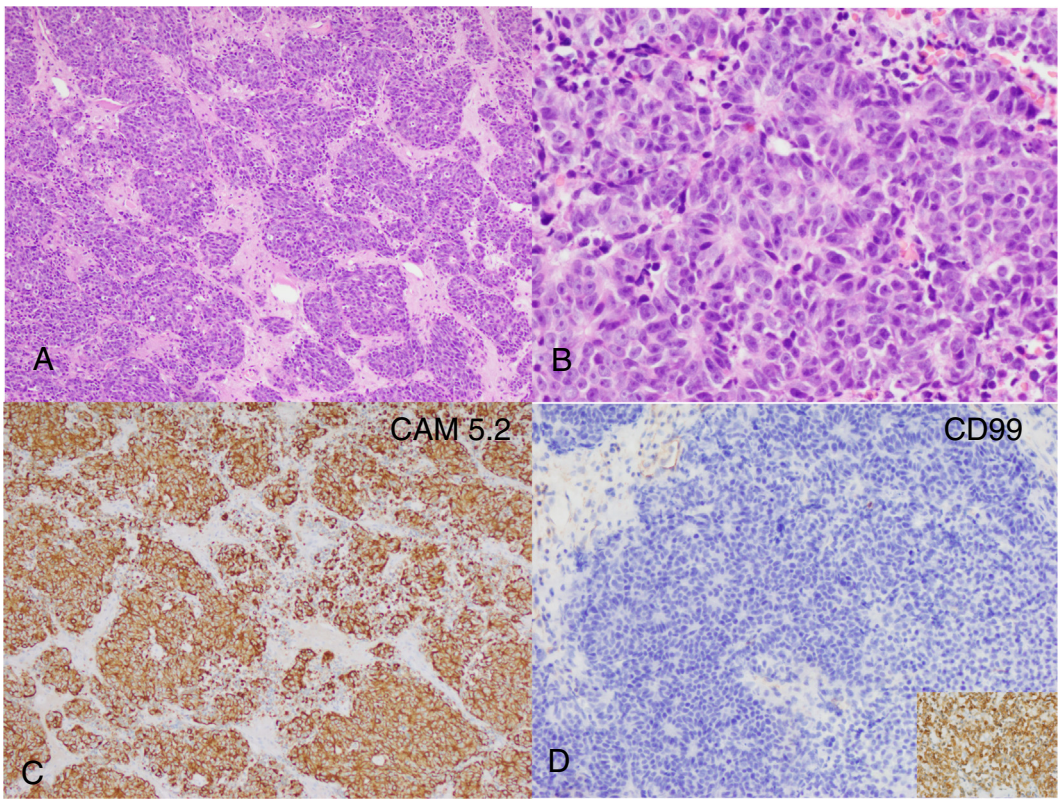

Fig. 2 SNUC with extensive rosette formation. A, High-grade blue cell proliferation with nested growth pattern (H&E, ×100). B, Rosette formation (H&E, ×200). Tumor cells were positive for CAM5.2 (C, ×100) and AE1/AE3 (not shown), and negative for CD99 (D, ×100; inset: CD99-positive control).

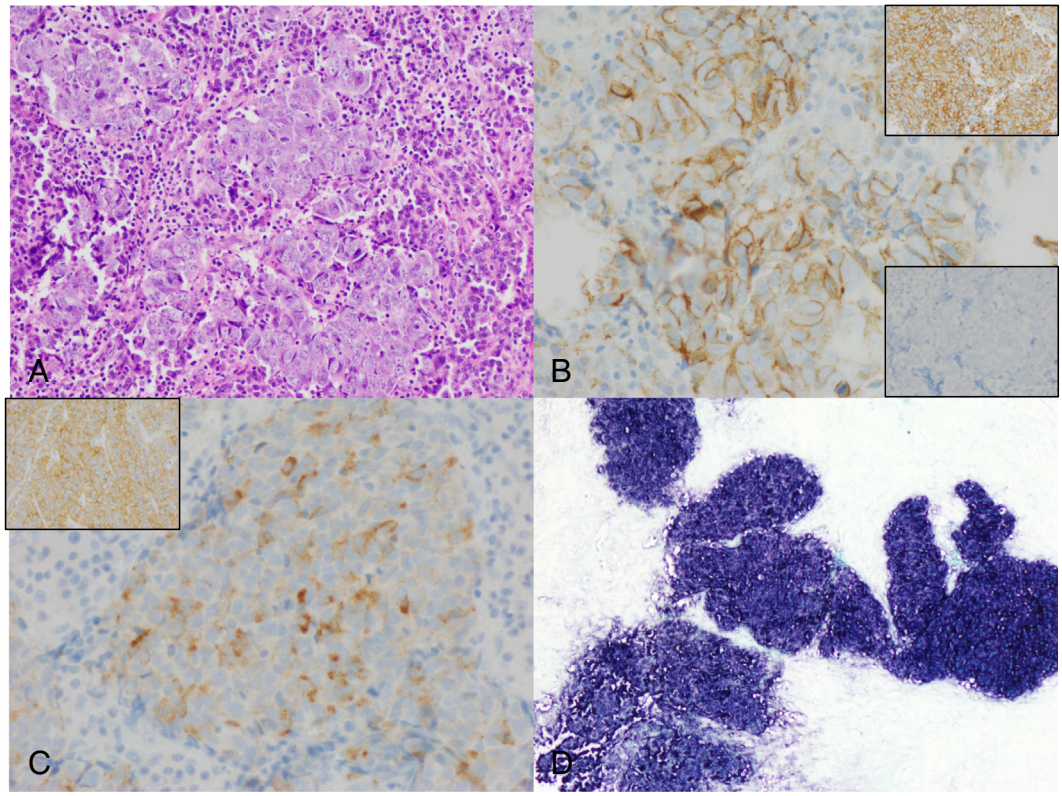

Fig. 3 EBV-positive LCNEC of the nasopharynx originally diagnosed as SNUC. A, Tumor cells with nested growth pattern and abundant lymhoplasmacytic infiltration (H&E, ×200). Tumor cells were positive for CD56 (B, ×200; inset: CD56-positive control; lower inset: negative control [mouse] antibody) and synaptophysin (C, ×200; inset: synaptophysin positive control), and EBER in situ hybridization was diffusely positive (D, ×100).

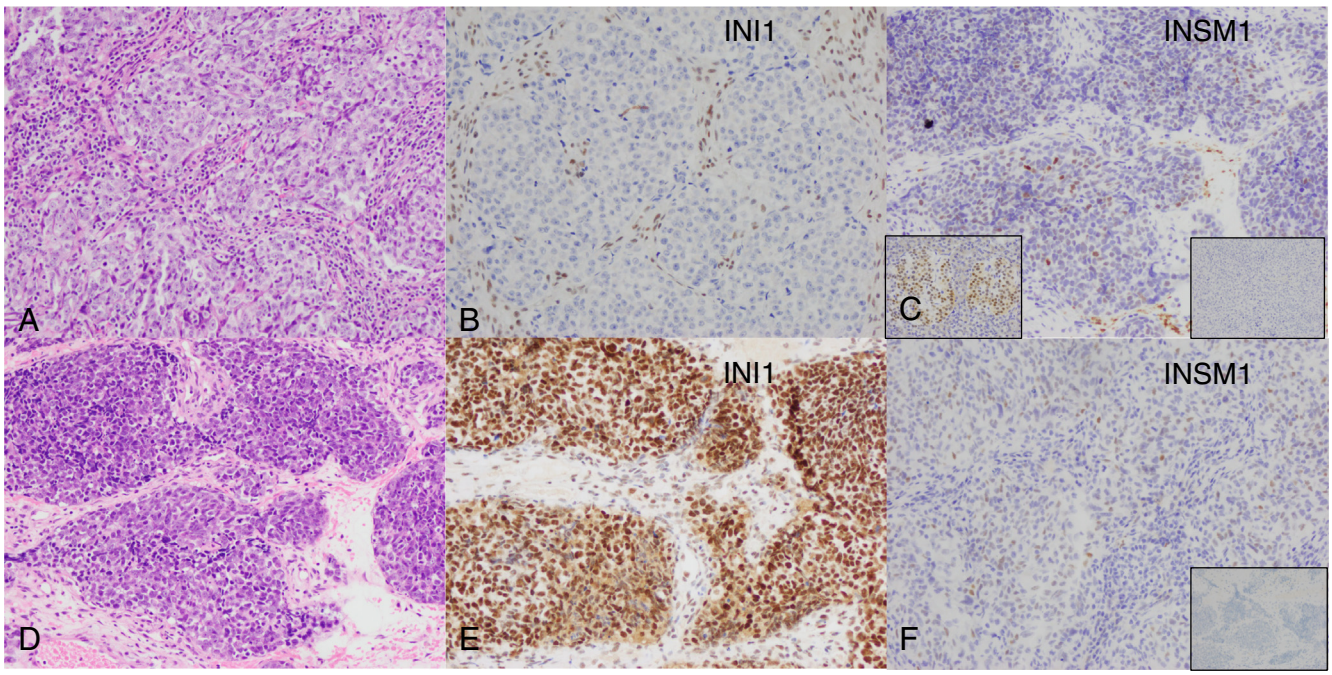

Fig. 4 SMARCB1-deficient sinonasal carcinoma (A) and SNUC (D). Immunohistochemical stain for INI1 showed loss of nuclear stain in SMARCB1-deficient sinonasal carcinoma (B), but retained in SNUC (E). Focal weak staining for INSM1 was seen in SMARCA1-deficient sinonasal carcinoma and SNUC (C and F; negative control right lower corner; INSM1 positive control left lower corner in picture C; ×200).

and 2 of 3 SMARCB1-deficient sinonasal carcinomas (Table).

Clinically, SNUC and SMARCB1-deficient carcinoma behaved in an aggressive manner. All patients presented with high-stage disease (stage III or IV; Table). Brain involvement was present as the initial presentation in 5 of 9 patients. One patient presented with metastatic disease involving the lung and liver. However, lymph node involvement was uncommon and seen only in 2 patients. Most of the patients were treated with combined surgery, chemotherapy, and radiation. Follow-up was available in 6 of these 11 patients. Despite multimodal treatment, patients with SNUC or SMARCB1-deficient carcinoma had poor prognosis (Table). In contrast, the patient with sinonasal LCNEC was disease-free after 7 years of initial diagnosis, and the patient with EBV-positive nasopharyngeal LCNEC showed complete clinical and radiologic response after combined chemoradiation therapy and was disease-free after 1 year of initial diagnosis (Table).

4. Discussion

Surgical pathology of the sinonasal tract is one of the most challenging fields owing to the tremendous diversity of tumors arising in this region [3]. Many of these tumors are very rare and can demonstrate overlapping histomorphologic features with one another. SNUC is one of the high-grade sinonasal carcinomas with a lengthy differential diagnoses, including squamous cell carcinoma, lymphoma, NEC, melanoma, and sarcoma. A panel of immunohistochemical studies including epithelial markers (pancytokeratins), neuroendocrine markers, skeletal muscle markers, lymphoma markers, and S100 are usually necessary for establishing the diagnosis [16]. SNUC is typically only positive for cytokeratins including AE1/AE3, CAM5.2, CK7, and CK18, and negative for other markers. Previous studies have reported that p16 and CD117 are positive in SNUC [1]. However, how these 2 markers can be helpful in diagnosing SNUC has not been explored. In this study, we found that CD117 was positive in all SNUC cases and negative in SNUC mimickers, and that p16 is positive in 5 of 6 cases of SNUC, suggesting that CD117 and p16 can be helpful with SNUC diagnosis. Importantly, it is worth mentioning that SNUC is not associated with human papillomavirus infection despite p16 positivity. When viral infection is detected (either human papillomavirus or EBV), the diagnosis of SNUC should be questioned [1].

Distinguishing SNUC from high-grade NEC can be challenging, yet important for prognostic and therapeutic purposes [17]. Neuroendocrine markers, including NSE, CD56, synaptophysin, and chromogranin, have limited sensitivity for high-grade NEC and can be expressed in a number of nonneuroendocrine tumors [17]. SNUC is typically positive for NSE and may be focally positive for synaptophysin and chromogranin. It is generally accepted that neuroendocrine morphology including organoid growth pattern, peripheral palisading, and rosette formation, in addition to positivity for neuroendocrine markers, is necessary for diagnosing NEC [18]. However, these features can sometimes be difficult to appreciate. SNUC often shows a nested growth pattern and sometimes with prominent festooning, which can be interpreted as organoid growth and peripheral palisading [17]. INSM1 is a recently developed marker with high sensitivity and specificity for head and neck neuroendocrine tumors [19]. In this study, we found that focal weak positivity for INSM1 is present in most of these 11 cases, including 5 of 6 SNUC cases. Strong, diffuse staining is seen in the case of sinonasal LCNEC, whereas only focal and weak positivity is present in the EBV-associated nasopharyngeal LCNEC. In these limited number of cases, it seems that for high-grade carcinomas, INSM1 does not demonstrate superiority over other conventional neuroendocrine markers.

SMARCB1 (INI-1)–deficient sinonasal carcinoma is a recently described entity characterized by loss of nuclear expression of SMARCB1. SMARCB1 is a protein component of the SWI/SNF nucleosome remodeling complex involved in the regulation of gene expression. SMARCB1-deficient sinonasal carcinoma has been shown to be a distinct entity with characteristic pathomorphologic features and an aggressive clinical behavior [11]. SMARCB1-deficient sinonasal carcinoma should be considered in any difficult-to-classify sinonasal carcinoma. In this study, we found that 3 (almost 30% of the cases) of 11 cases with an original diagnosis of SNUC showed loss of SMARCB1 nuclear expression upon further testing. Thus, it is reasonable to suggest that a diagnosis of SNUC should be made only after SMARCB1-deficient sinonasal carcinoma has been ruled out, especially for tumors with moderate amount of eosinophilic cytoplasm [20].

SMARCA4 and ARID1A are 2 other subunits of the SW1/SNF complex. Loss of SMARCA4 expression has been identified in highly aggressive tumors including hypercalcemic-type small cell carcinoma of the ovary, SMARCA4-deficient thoracic sarcoma, and SMARCA4-deficient undifferentiated uterine sarcoma [21-23]. A recent study showed that SMARCA4 loss was detected in one case of SNUC [12]. ARID1A is the most frequently mutated subunit of the SWI/SNF complex. Loss of ARID1A expression is found in colorectal carcinoma, ovarian carcinoma, endometrial carcinoma, and others, but has not been reported in SNUC [24]. In this study, none of these 11 cases showed loss of SMARCA4 or ARID1A expression, suggesting that SMARCA4- or ARID1A-deficient sinonasal carcinoma is probably uncommon.

NUT carcinoma is a rare high-grade tumor that can occur in sinonasal tract. NUT carcinoma is defined as poorly differentiated squamous cell carcinoma with NUTM1 gene rearrangement [1,9]. Morphologically, NUT carcinoma consists of sheets of undifferentiated blue cells with necrosis, and brisk mitotic and apoptotic activity. Some cases show squamous differentiation in the form of “abrupt foci of keratinization.” Immunohistochemically, NUT carcinoma is positive

for cytokeratin markers and squamous markers such as p63, p40, and CK5/6. Positive immunohistochemical staining for NUT and/or molecular demonstration of NUTM1 gene rearrangement are required for diagnosis [1]. In this study, immunohistochemical stain for NUT was negative in all 11 cases. Because NUT carcinoma is positive for squamous markers, it is more likely to be diagnosed as poorly differentiated squamous cell carcinoma rather than SNUC.

One of the SNUC cases in this study showed rosette formation. Rosette architecture is typically seen in tumors with neural or neuroendocrine differentiation and can also be seen in Ewing sarcoma, melanoma, and Wilm's tumor. Rosette formation has not been reported in SNUC and was considered a useful morphologic feature to distinguish neuroblastoma from SNUC [17]. The case in this study was negative for all neural or neuroendocrine markers, arguing against neuroblastoma; and was diffusely positive for cytokeratins, p16, and CD117, immunohistochemically consistent with SNUC. Because the presence of rosette formation does not exclude an SNUC diagnosis according to the current diagnostic definition, and this case is truly "otherwise unclassifiable," an SNUC diagnosis is appropriate in this setting.

In summary, we found that a significant portion of cases with original diagnosis of SNUC were reclassified into specific entities, such as high-grade NEC, SMARCB1-deficient carcinoma, and EBV-positive nasopharyngeal LCNEC. Distinguishing these specific entities from SNUC is crucial for optimal clinical management and for further delineation of these rare and likely underdiagnosed diseases.

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