Sinonasal Undifferentiated Carcinoma (SNUC): From an Entity to Morphologic Pattern and Back Again—A Historical Perspective

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Abstract: Since the first description of sinonasal undifferentiated carcinoma (SNUC) as a distinctive highly aggressive sinonasal neoplasm with probable origin from the sinonasal mucosa (Schneiderian epithelium), SNUC has been the subject of ongoing study and controversy. In particular, the SNUC category gradually became a "wastebasket" for any undifferentiated or unclassifiable sinonasal malignancy of definite or probable epithelial origin. However, with the availability of more specific and sensitive immunohistochemical antibodies and increasing implementation of novel genetic tools, the historical SNUC category became the subject of progressive subdivision leading to recognition of specific genetically defined, reproducible subtypes. These recently recognized entities are characterized by distinctive genetic aberrations including *NUTM1*-rearranged carcinoma (NUT carcinoma) and carcinomas associated with inactivation of different members of the *SWI/SNF* chromatin-remodeling gene complex such as SMARCB1-deficient and less frequently SMARCA4-deficient carcinoma. The ring became almost closed, with recent studies highlighting frequent oncogenic *IDH2* mutations in the vast majority of histologically defined SNUCs, with a frequency of 82%. A review of these cases suggests the possibility that "true SNUC" probably represents a distinctive neoplastic disease entity, morphologically, phenotypically, and genetically. This review addresses this topic from a historical perspective, with a focus on recently recognized genetically defined subsets within the SNUC spectrum.

Key Words: sinonasal undifferentiated carcinoma, NUT carcinoma, SMARCB1-deficient carcinoma, SMARCA4-deficient carcinoma, olfactory neuroblastoma, teratocarcinosarcoma, IDH2, mutation, SMARCB1 protein

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In 1986, members of the head and neck pathology group from the University of Virginia described a series of 8 highly aggressive sinonasal carcinomas occurring over a wide age range (30 to 77 y) and presenting as locally advanced masses involving multiple sinonasal cavities (nasal cavity, maxillary antrum, and ethmoid sinus) and frequently extending into the orbital tissue and the cranial cavity.[1] The majority of affected patients (5/8) died at a mean of 4 months after diagnosis.[1] Histologically, these neoplasms were characterized by a particular architecture (nests, wide trabeculae, ribbons, sheets, and vague organoid pattern), cytomorphology (medium to large cells with round-oval nuclei, vesicular chromatin, variable nucleolar prominence, and small to moderate rim of eosinophilic cytoplasm), high-grade features (high mitotic rate, frequent tumor necrosis, and prominent vascular permeation), epithelial phenotype (immunoreactivity for cytokeratin and/or epithelial membrane antigen, and presence of small desmosomes on electron microscopy), subtle neuroendocrine traits (partial reactivity for neuron-specific enolase and the presence of rare membrane-bound dense-core granules ultrastructurally), and the absence of squamous, glandular, or neuroblastic differentiation (Fig. 1).[1] The authors proposed the term *sinonasal undifferentiated carcinoma* (SNUC) for this "*highly distinctive clinicopathologic entity*" to distinguish it from other, less aggressive sinonasal malignancies. Follow-up studies on small series from the same group and others confirmed SNUC as a distinctive sinonasal entity and tried to define potential etiological disease factors and prognostic parameters.[2,3]

SINONASAL UNDIFFERENTIATED CARCINOMA: EPIDEMIOLOGICAL AND SURVIVAL DATA

Although reliably reproducible epidemiological studies applying strict diagnostic criteria are lacking, SNUCs are rare

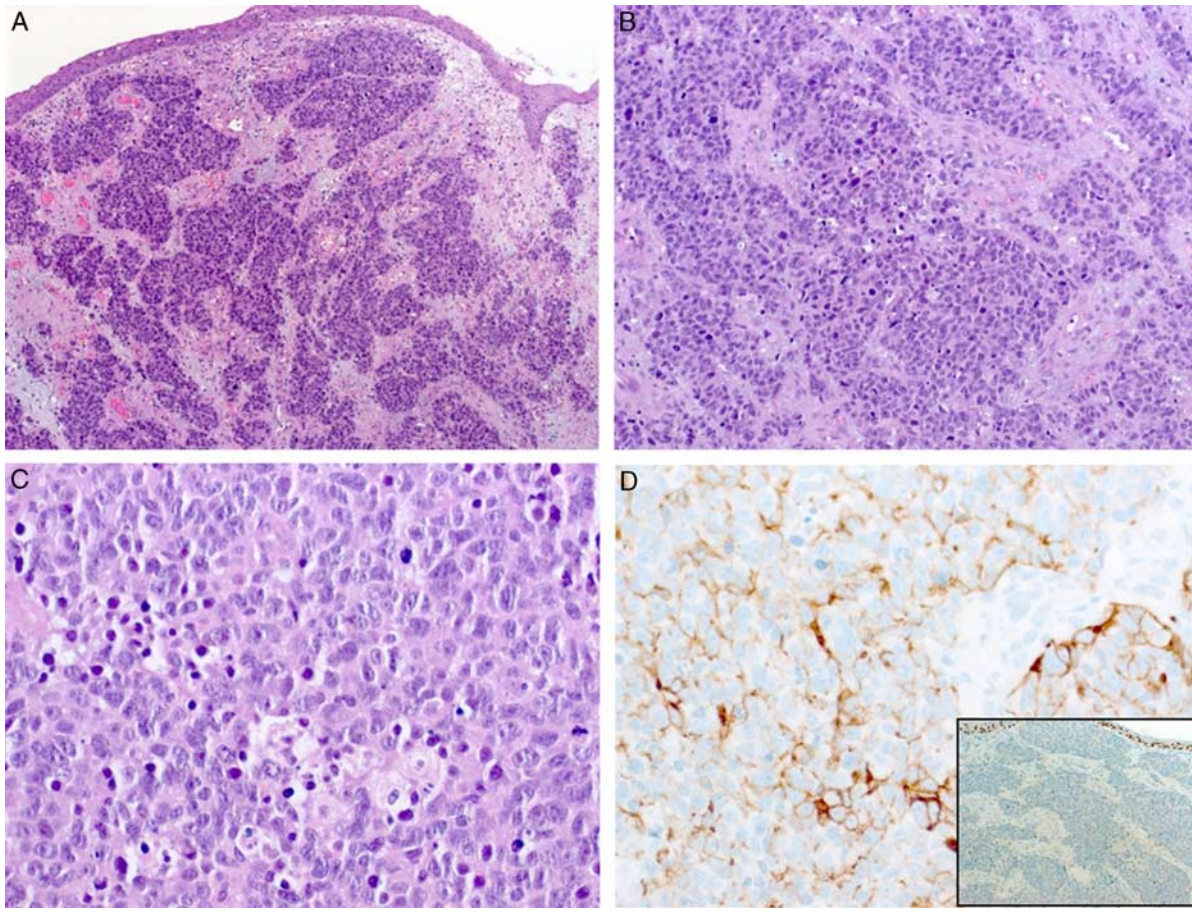

FIGURE 1. *IDH2*-mutant sinonasal undifferentiated carcinoma shows irregular interconnected nests and strands of undifferentiated tumor cells beneath the respiratory mucosa, which shows metaplastic but lacks dysplastic changes (A). B and C, Higher magnification illustrating polygonal cells with prominent nucleoli and single-cell necrosis; note absence of squamoid or glandular features. D, pan-cytokeratin (AE1/AE3) is variably expressed. p40 is positive only in the covering mucosa (inset).

with <400 cases documented in the literature since the original series.[4] According to the Surveillance, Epidemiology, and End Results (SEER) database, the age-adjusted incidence rate of SNUC is 0.02 per 100,000, higher in male individuals (0.03) than in female individuals (0.01).[4] SNUC carries a dismal prognosis,[1] although showing improvement, possibly attributable to the adoption of more aggressive multimodal therapy regimens incorporating intensified radiotherapy and/or chemotherapy after surgery.[5–9] In a recent review of the SEER database, the overall 5- and 10-year relative survival rates for SNUC patients were 34.9% and 31.3%, respectively.[4] The overall median survival was improved when surgery was combined with irradiation (22.1 vs. 41.9 mo).[4] The 5-year relative survival rates following surgery, irradiation, or surgery combined with irradiation were 38.7%, 36.0%, and 39.1%, respectively.[4] The median survival seems to be improving from 14.5 months during 1973-1986 to 23.5 months during 1987-2010.[4] However, it remains unclear whether histologic and genetic subtypes in the historical SNUC spectrum, as discussed below (including variants associated with no or poor response to conventional chemotherapy such as NUT carcinomas and those with paradoxically better response to radiochemotherapy, as observed in some SMARCB1-deficient carcinomas), may account for the heterogeneity in outcome data.

Defining Sinonasal Undifferentiated Carcinoma: From Current Vague Concept Back to Precise Original Definition

Lack of Specific Line of Differentiation

Although in the original description not all undifferentiated (anaplastic) sinonasal carcinomas were considered SNUCs,[1] over time, absence of a specific line of differentiation became the diagnostic feature of SNUC, and the current World Health Organization (WHO) classification defines SNUC as "undifferentiated epithelial neoplasm (carcinoma) lacking evidence of squamous or glandular differentiation by histology and immunophenotyping, in a sense of undifferentiated carcinoma, not otherwise specified."[10] Endorsing an exclusion-based diagnostic algorithm would be significantly influenced by the subjectivity in recognizing some differentiating morphologic features and the availability and/or extent of diagnostic (immunohistochemical, electron microscopic, and/or genetic) markers. In this context, several poorly differentiated neoplasms, although not prototypical SNUC on H&E staining, have been allocated to the SNUC category on the basis of evidence of epithelial differentiation (eg, cytokeratin immunoreactivity) and lack of other specific (squamous or

glandular) lines of differentiation. This made SNUC a morphologic pattern or final pathway of dedifferentiation, becoming an undifferentiated carcinoma not otherwise specified, in contrast to the original proposal of a distinctive entity.[1]

In contrast to poorly differentiated and nonkeratinizing squamous cell carcinoma and nasopharyngeal-type carcinoma, which frequently express CK5/6, SNUC showed only low–molecular-weight keratin expression (such as CK8, CAM5.2).[11] CK7 was expressed in half of SNUC and squamous cell carcinoma cases.[11] The simple epithelial phenotype has been confirmed by other studies, which also showed minimal to absent expression of p40.[12]

This simple epithelial phenotype is, however, complicated by 2 major factors: (1) comparable cytokeratin profiles (with or without neuroendocrine traits) have been often recognized in poorly differentiated mesenchymal malignancies, like solid-pattern alveolar rhabdomyosarcomas[13] and subsets of Ewing family tumors,[14] which can be misinterpreted as SNUC or poorly differentiated carcinoma; and (2) some squamous cell carcinomas and high-grade non–intestinal-type adenocarcinomas may show transition to an undifferentiated phenotype (in the sense of dedifferentiation) accompanied by loss of most of the characteristic immunoreactivities and thus displaying a simple cytokeratin profile closely mimicking SNUC on biopsy.[15] These observations support the need for applying a rather wide immunohistochemical panel for the differential diagnostic workup of any potential SNUC, especially adequately sampling resection specimens.

Subtle Neuroendocrine Traits in Sinonasal Undifferentiated Carcinoma

These findings were acknowledged in the original SNUC description[1] and still represent a potential source of confusion with high-grade olfactory neuroblastoma (ONB) and neuroendocrine carcinoma. High-grade (Hyams grade 3 and 4) ONB has been frequently given preference over SNUC (more frequently by neuropathologists than by head and neck pathologists).[16,17] In a recent study utilizing unsupervised hierarchical clustering analysis of the DNA methylation data of cases originally diagnosed as ONB, 11% proved to be *isocitrate dehydrogenase* (*IDH*)-mutated SNUCs.[16] In 2 reviewed series (1 by conventional pathology, the other by methylation analyses), only 16% and 64% of institutionally diagnosed ONB represented genuine ONB cases, respectively.[16,17] Although ONB is essentially cytokeratin-poor, rare cases with variable cytokeratin reactivity may be seen. Hyams grade 4 ONB should be diagnosed rarely and only after excluding other tumors, as there is a significant overlap with SNUC and poorly differentiated neuroendocrine carcinomas.[16–18]

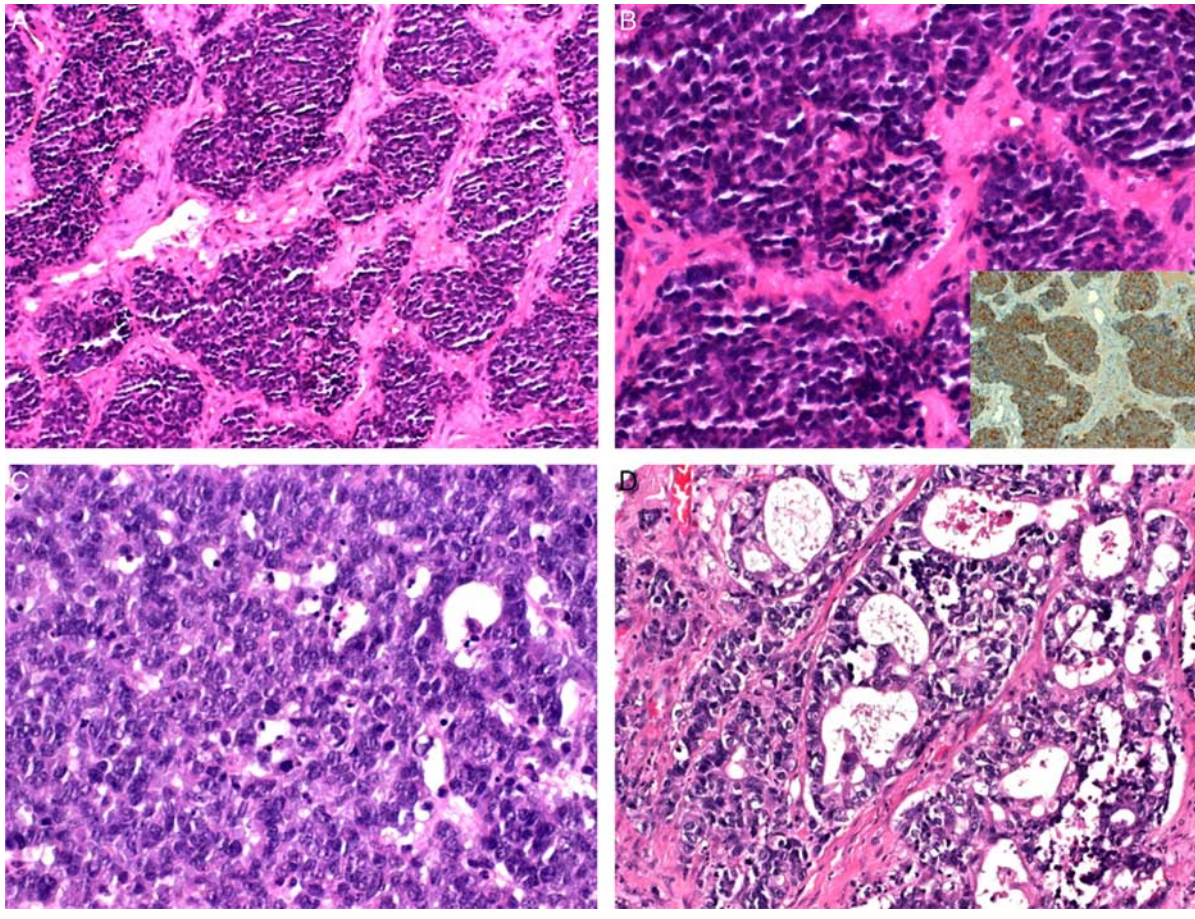

FIGURE 2. Sinonasal undifferentiated carcinoma mimics. This high-grade non–intestinal-type adenocarcinoma has areas indistinguishable from sinonasal undifferentiated carcinoma (A–C; initial biopsy), but shows a prominent glandular pattern in the resection specimen (D), underlining the need for sufficient sampling. Diffuse pancytokeratin expression is illustrated in (B, inset).

High-grade non–intestinal-type sinonasal adenocarcinoma (non-ITAC) is still a vaguely-defined rare neoplastic category that may overlap with SNUC and high-grade ONB.[19] Admittedly, the distinction may be impossible on limited biopsy material, as SNUC-simulating areas may be seen in gland-poor areas of high-grade non-ITAC (Fig. 2).[19] It has been reported that SNUC may recur as non-ITAC.[20] These observations suggest that high-grade non-ITAC may be misinterpreted as SNUC on initial, limited biopsy material.

Sinonasal Undifferentiated Carcinoma Definition: Exclude Dedifferentiated Carcinoma

As stated above, the mere expression of simple cytokeratins in an otherwise undifferentiated non–small cell malignancy may raise the possibility of SNUC. Sampling errors must be considered. Various tumors including squamous cell carcinoma, human papillomavirus (HPV)-related multiphenotypic sinonasal carcinoma, high-grade non-ITAC, teratocarcinosarcoma, and others may show SNUC-like areas that do not express more than simple cytokeratins. In addition, rare SNUC-type carcinomas have been reported to originate in association with or from sinonasal papilloma and gliomatosis.[21–23] Thus, sufficient sampling of resections is mandatory to exclude such possibilities.

Sinonasal Undifferentiated Carcinoma Definition: Lack of Specific Etiological Factors

In contrast to nasopharyngeal-type lymphoepithelial carcinoma, SNUC has been consistently Epstein-Barr virus (EBV)-negative.[24] However, Lopatequi et al[25] identified EBV RNA (EBER1) in 7 of 11 SNUCs from Asian, but in no SNUCs from Western patients. These authors discussed genetic predisposition and/or environmental and geographical factors that may influence the strength of the association of SNUC with EBV.[25] Data on the role of HPV and p16 in SNUC have been heterogenous and controversial, and, to date, no study has investigated the transcriptional activity of the rare HPV-positive SNUCs (Table 1).[26–29] It is, therefore, not excluded that some of these cases might have represented the least differentiated variants on the spectrum of HPV-related carcinomas[30] rather than true SNUCs, but this remains speculative. The frequency of p16 expression in SNUC ranges from 20% to 100%, and it does not predict the HPV status (Table 1).[26–29] This highlights the limitation of p16 as a maker to distinguish HPV-related multiphenotypic sinonasal carcinoma from SNUC.

Sinonasal Undifferentiated Carcinoma Definition: Exclusion of Specific Genotypes in the Heterogenous Sinonasal Undifferentiated Carcinoma Category

With the availability of newer immunohistochemical antibodies and increasing implementation of novel genetic tools, it became evident that some neoplasms included in the historical SNUC spectrum can be redefined by reproducible phenotypic and genetic findings (Tables 2, 3).

NUT carcinoma (NUT midline carcinoma) is a highly aggressive carcinoma defined by the fusion of the *NUT* (*NUTM1*) *gene* on chromosome 15q14 with *BRD4* on chromosome 19p13, resulting in the t(15;19) translocation.[32] Rare tumors harbor *NUT-BRD3*, *NUT-NSD3*, or other rare variants.[32] The first sinonasal NUT carcinoma was identified in 2004.[32] Given that 20% of EBV-negative undifferentiated carcinomas of the upper aerodigestive tract were found to harbor *NUT* gene rearrangements by fluorescence in situ hybridization (FISH),[33] NUT carcinoma is likely under-recognized, which may account for the low number of reported cases.[33,34] NUT carcinoma represents ~2% of all primary sinonasal carcinomas and 15% of SNUC-like tumors.[34] As NUT carcinomas are indistinguishable from other poorly differentiated or undifferentiated carcinomas, the use of NUT immunohistochemistry has been encouraged on any undifferentiated sinonasal malignancy that is not otherwise easily classifiable into a specific category (Fig. 3).[34] Occasional presence of abrupt squamous differentiation and frequent expression of p40/p63 is the major cause for misdiagnosis as poorly differentiated non-keratinizing/basaloid squamous cell carcinoma. Rare cases are p40-negative or p63-negative, complicating the differential with SNUC.[12] Although distinction from SNUC may be rather arbitrary, detection of abrupt squamous differentiation should favor NUT carcinoma.[33,34] The frequency of squamous differentiation as a clue to NUT carcinoma varied from <50% to 82% of cases, but this feature might have been overrepresented, as tumors lacking this histologic pattern might go undetected if the NUT immunohistochemistry is not performed. Finally, the median age is lower in sinonasal NUT carcinoma compared with SNUC (36 vs. 53 y, respectively). Notably, > 50% of SNUCs diagnosed in patients younger than 50 years were ultimately reclassified as NUT carcinomas.[33,34]

SMARCB1-deficient sinonasal carcinoma has been recently recognized as a distinct entity defined by loss of SMARCB1 (INI1) protein expression, a member of the chromatin-remodeling SWI/SNF complex. To date, some 70 cases have been reported.[35–39] The tumors developed in patients over a wide age range (19 to 89 y; median 52) with a slight predilection for male individuals. Almost all patients presented with advanced local disease (cT4) and received surgery combined with chemoradiation in most cases; hence, the significant differences in outcome cannot be explained on the basis of disease stage and treatment modality alone.[35–39] Slightly more than half of the patients died at a median of 15 months (range, 0 to 102 mo). Similarly, the original diagnosis was SNUC in 36% of cases.[38] The majority (60%) of sinonasal SMARCB1-deficient carcinomas displayed nondescript undifferentiated basaloid morphology, often with rhabdoid or plasmacytoid cytology. Indeed, these tumors often resemble basaloid squamous cell carcinoma rather than SNUC (Figs. 4A–C).[35–39]

The biology seems to be heterogenous, as there were several patients with similarly advanced disease stage at initial diagnosis, and yet survived for several years following aggressive multimodal therapy (longest survival 21 y; Agaimy et al.[31] Although insufficient data are available, there is initial evidence that nonmetastatic basaloid morphology cases that receive aggressive postsurgical chemoradiation tend to have a better outcome and that single cases show a dramatic response to preoperative chemoradiation.[38]

TABLE 1. p16 and Human Papillomavirus Status in Sinonasal Undifferentiated Carcinoma (SNUC)

References	SNUC Cases	p16 Positive (%)	Human Papillomavirus Positive
El-Mofty and Lu[26]	10	2 (20)	1
Wadsworth et al[27]	5	5 (100)	0
Bishop et al[28]	16	4 (25)	1
Gray et al[29]	14	11 (78)	9
Total	45	22 (49)	11 (24)

TABLE 2. Recently Identified Genotypic Categories in the Historical SNUC spectrum

Entity	Originally Diagnosed as SNUC (%)	Of Institutional SNUC Cohort (%)	All Sinonasal Carcinomas (%)	Genotype	Frequency of Genotype (%)
NUT carcinoma	66	15	~1	*NUT-BRD4*, *NUT-BRD3*, *NUT-NSD3* gene fusions	100 (definitional)
SMARCB1-deficient carcinoma	36	14	~5	*SMARCB1* inactivation (loss by IHC)	100 (definitional)
SMARCA4-deficient carcinoma	50	9	<1	*SMARCA4* inactivation (loss by IHC)	100 (definitional)
IDH2-mutated SNUC	100	49-82	~27*	activating *IDH2* mutations	49-82

*Biased due to the inclusion of consult cases.
IDH indicates isocitrate dehydrogenase; IHC, immunohistochemistry; SNUC, sinonasal undifferentiated carcinoma.

The immunoprofile of sinonasal SMARCB1-deficient carcinoma is heterogenous with the consistent expression of pankeratin but with variable reactivity for CK5 (64%), p63 (55%), CK7 (48%), and neuroendocrine markers.[38] FISH analysis confirmed deletions of the *SMARCB1 gene* locus in 78% of cases.[38] The mechanisms of *SMARCB1* inactivation in those FISH-negative cases are likely inactivating mutations not detectable by FISH, although epigenetic alterations may also be involved.[40] Because of the complexity and heterogeneity of molecular mechanisms, SMARCB1 immunohistochemistry has emerged as a most valuable, sensitive, and specific tool in identifying these tumors, irrespective of the exact genetic mechanisms underlying the SMARCB1 gene silencing. SMARCB1-deficient sinonasal carcinoma represents an emerging entity, temporarily included with SNUC in the current WHO classification.[10]

SMARCA4-deficient Sinonasal Carcinoma

SMARCA4 loss represents an alternative genetic defect in histologically comparable carcinomas with retained SMARCB1 expression. To date, 2 cases have been described[41,42] (a series of 10 cases has been submitted by Agaimy et al).[31] SMARCA4-deficient sinonasal carcinomas are similar to the SMARCB1-deficient cases but show a higher degree of overlap with SNUC and poorly differentiated neuroendocrine carcinomas (Figs. 4D–F). Their frequency is unknown, although they represented 9% of all SNUC-like tumors and 20% of *IDH2* wild-type SNUC-like tumors in 1 study.[41]

Sinonasal Undifferentiated Carcinoma Definition: *IDH2* Mutations in Sinonasal Undifferentiated Carcinoma

As integral components of the Krebs cycle, the metabolic enzymes IDH1 and IDH2 catalyze the conversion of isocitrate to α-ketoglutarate associated with a reduction of NADP to NADPH.[43] Hotspot oncogenic (activating) point mutations in *IDH1 and IDH2* occur regularly across different tumor entities including, in particular, subsets of low-grade gliomas/secondary glioblastoma, chondrosarcoma, small duct intrahepatic cholangiocarcinoma, and hematological malignancies among others.[43] Via altering vital cellular processes such as epigenetic regulation and metabolism, oncogenic *IDH* mutations are closely involved in the process of cancer cell differentiation.[43] In vitro and in vivo preclinical studies and ongoing clinical trials demonstrated promising results for novel drugs targeting mutant IDH1/2.[43]

Using targeted next-generation sequencing of 300 cancer-related genes, Jo et al[41] detected *IDH2* R172X mutations in 55% of 11 SNUCs. They also confirmed the

TABLE 3. Clinicopathologic Features of Sinonasal Undifferentiated Carcinoma Compared With NUT Carcinoma and SWI/SNF-Deficient Carcinoma

Features/Entity	SNUC All	NUT Carcinoma	SMARCB1-Deficient Carcinoma	SMARCA4-Deficient Carcinoma
Age [range (median)] (y)	30-77 (53)	26-48 (33)	19-89 (52)	20-67 (44)
Male:female ratio	1:1.6	3:0	1.4:1	2.3:1
Site	Nasal cavity, maxillary sinus, ethmoid, less frequent others	Sinuses (mainly maxillary +ethmoid)	Sinuses (mainly ethmoid): 50%; nasal cavity +/− sinuses: 50%	Mainly nasal cavity, then nose+sinuses
Death due to disease (%)	62.5	100	54	67†
Time to death [range (median)] (mo)	1-41 (4)	8-16 (12)	0-102 (15)	1-7 (3)
p63 expression (%)	0	67	55	0
Neuroendocrine marker expression (%)	NA*	33 (focal)	25 (focal)	90 (focal)

*Sparse neuroendocrine-type dense core granules were seen in single cells of 5 cases examined by electron microscopy in the original description.[1]
†Only limited follow-up data available (all were under palliative treatment; based on Agaimy et al).[31]
NA indicates not available; SNUC, sinonasal undifferentiated carcinoma.

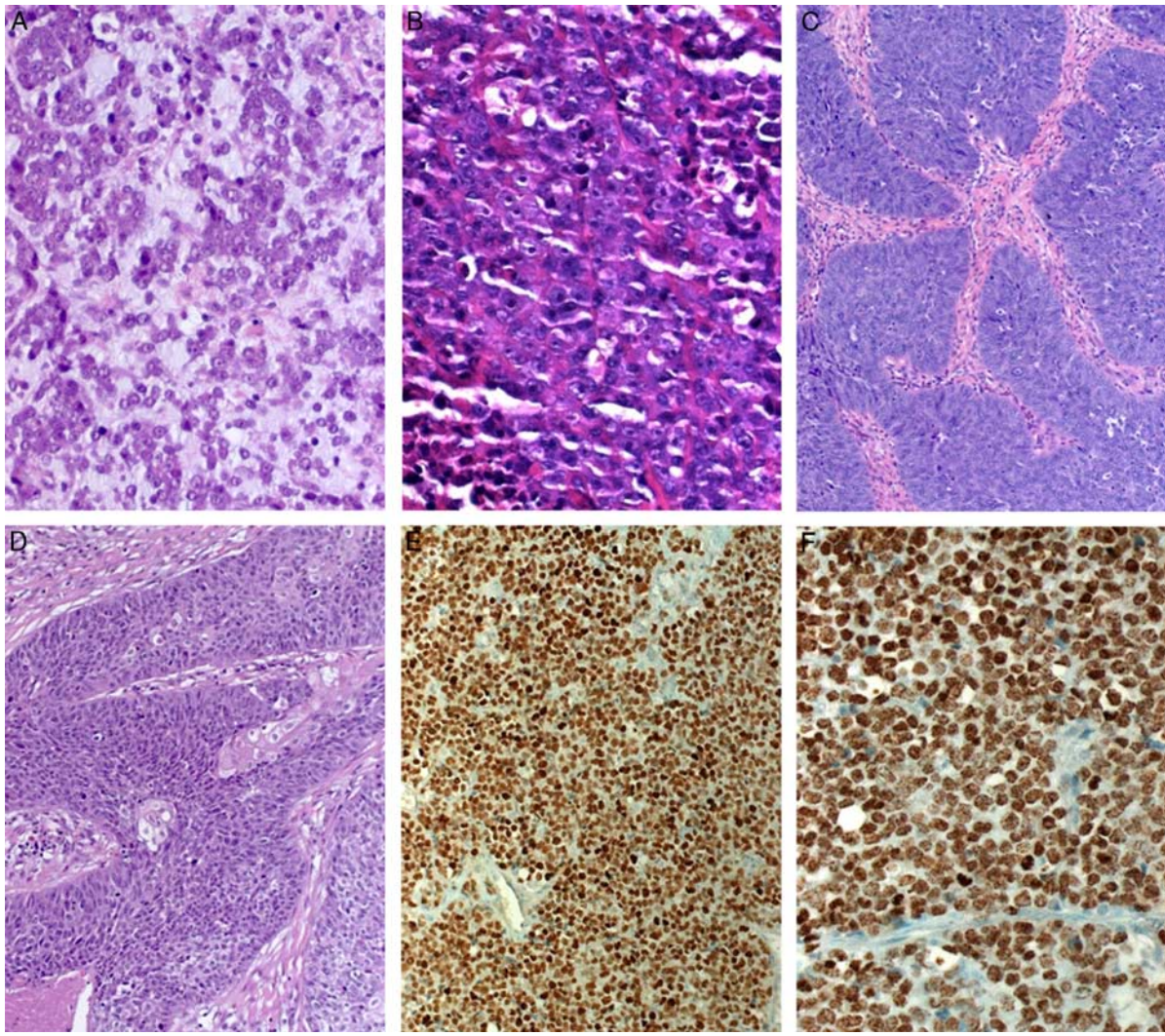

FIGURE 3. Sinonasal NUT carcinoma may display either small round (A) or large epithelioid (B) anaplastic cell pattern lacking any differentiating features except for rare variants with either diffuse basaloid squamous cell carcinoma–like (C) or minimal abrupt squamous or clear cell differentiation (D). Two thirds of cases express strongly p63 (E). Distinctive punctate nuclear reactivity with the NUT monoclonal antibody is definitional (100% of cases; F).

expression of the mutant IDH2 protein using the multi-specific mutant IDH1/2 immunohistochemistry.[41] Notably, *IDH* wild-type tumors harbored other genetic aberrations including 1 case with *SMARCA4*-inactivating mutation causing protein loss verified by immunohistochemistry.[41] The authors concluded that *IDH2* R172X mutations are specific to SNUC among head and neck carcinomas, which supports SNUC as a distinct clinicopathologic entity. *IDH*-activating mutations were absent in the authors' institutional head and neck cohorts of 412 head and neck cancers.[41] Follow-up studies uncovered a higher frequency of *IDH2* mutations in SNUC (up to 82.4% of morphologically defined SNUCs).[44–47] SWI/SNF inactivation (*SMARCB1* and *SMARCA4*) and *IDH2* mutations seem mutually exclusive, which indicates true driver genetic events in the harboring tumors.[44–47] Likewise, in methylation analyses, SNUC clustered differently from SMARCB1-deficient carcinomas, small cell neuroendocrine carcinoma, and ONB, indicating separate entities.[47] In recent studies, *IDH2* R172 and *IDH1* R132S mutations were virtually absent in >1000 cases of 8 different types of malignancies included in the differential diagnosis of SNUC.[46,47]

Sinonasal Undifferentiated Carcinoma Versus Poorly Differentiated (Large Cell) Neuroendocrine Carcinoma (LCNEC)

LCNEC may closely mimic SNUC. As already noticed, subtle neuroendocrine traits in the form of some architectural (cords, nests, and ribbons), immunophenotypic (partial reactivity for neuron-specific enolase), and ultrastructural (presence of rare or scattered membrane-bound dense-core granules) features have been detected in SNUC.[1] In line with the notion raised by Mills that at least a subset of SNUC "*fits broadly into the category of large cell neuroendocrine carcinoma*,"[48] recent studies showed some LCNEC clusters with *IDH2*-mutated SNUC.[48] Furthermore, 50% to 100% of the limited LCNEC cases examined in 3 studies harbored similar

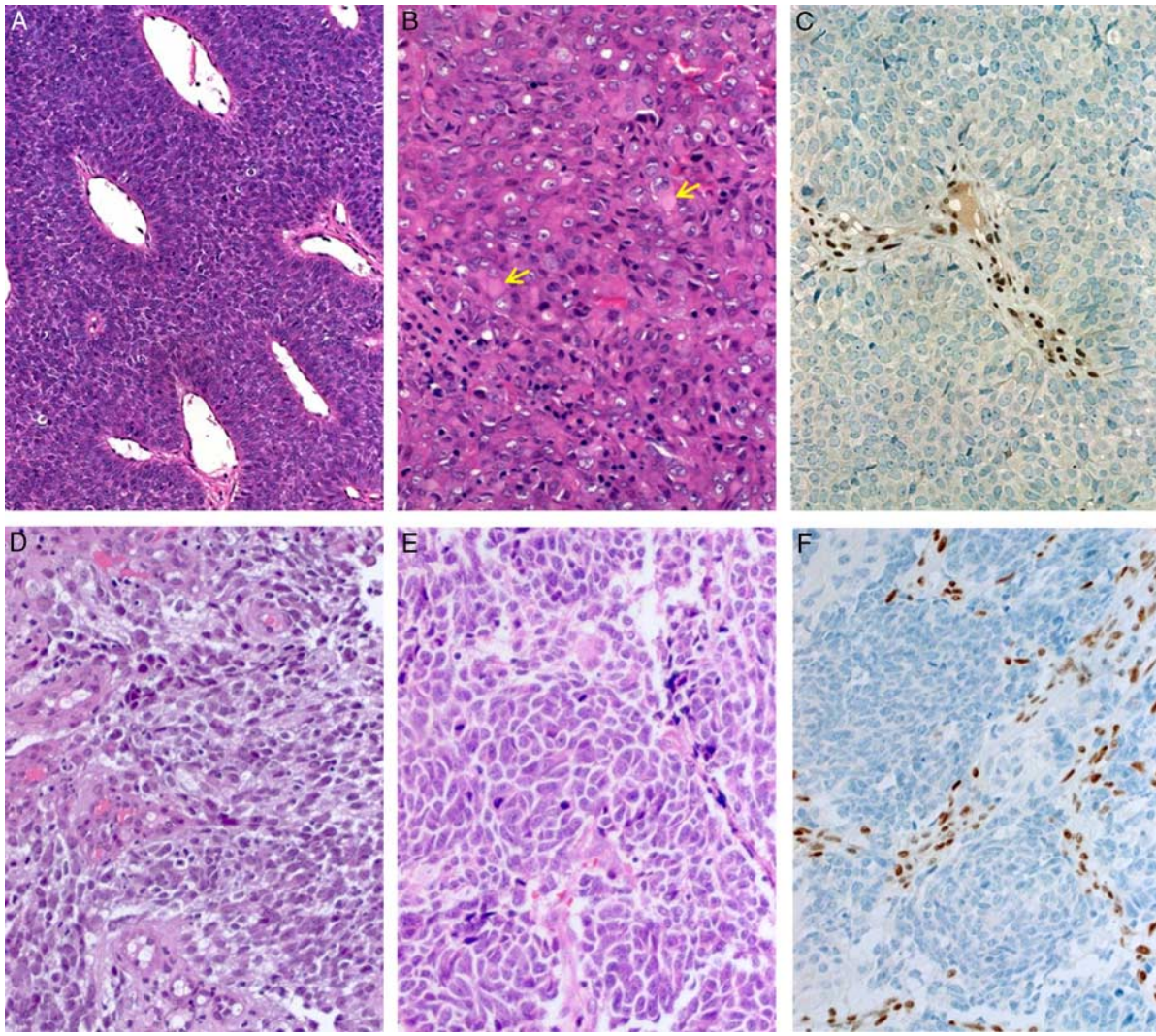

FIGURE 4. SWI/SNF-deficient sinonasal carcinomas. SMARCB1-deficient carcinomas display more frequently basaloid (A) and occasional eosinophilic/rhabdoid (B) morphology with monotonous cytology lacking bizarre-looking nuclei (a few rhabdoid inclusions are highlighted by arrows). C, Loss of SMARCB1 with retained expression in the background stromal cells is definitional. SMARCA4-deficient tumors tend to feature either small cell carcinoma–like (D) or large cell sinonasal undifferentiated carcinoma–like (E) morphology. The loss of SMARCA4 is diagnostic (F).

IDH2 mutations as SNUC.[44,46,47] On the basis of these observations and methylation studies, some authors speculated that *IDH2*-mutated SNUC and LCNEC likely represent a phenotypic spectrum of the same entity. On the basis of current data, the question as to whether SNUC and LCNEC represent variants of a single entity or different diseases sharing the same genetic defect remains to be resolved. Although it is evident that SNUCs are not LCNECs, some LCNEC cases may reflect SNUC with significant neuroendocrine differentiation.

Tracing Sinonasal Undifferentiated Carcinomas Back to Their Origin: Pattern or Entity?

On the one hand, the authors of the seminal SNUC publication emphasized the presence of a sinonasal anaplastic carcinoma spectrum and that these anaplastic carcinomas (in contrast to genuine SNUC) contain both small and large cell populations. On the other hand, they admitted the presence of different antigenicity subgroups within the morphologically homogeneous SNUC and considered the poor differentiation as a possible explanation for the heterogenous antigenicity. Of note, the difficulty in diagnosing SNUC on morphologic grounds alone was emphasized in that publication.[1] On the basis of current knowledge, 4 questions are raised regarding whether (1) to diagnose SNUC as an entity exclusively on the basis of morphology and immunophenotype irrespective of genotypes; (2) to consider SNUC as a morphologic spectrum of a genetically heterogenous disease with referral to identified specific genetic defects affecting variants within its spectrum; (3) to recognize those variants with specific genotypes (such as SWI/SNF-deficiency) as distinctive diseases unrelated to SNUC and consider SNUC a diagnosis of exclusion; or (4) to consider SNUC as a distinctive clinicopathologic entity

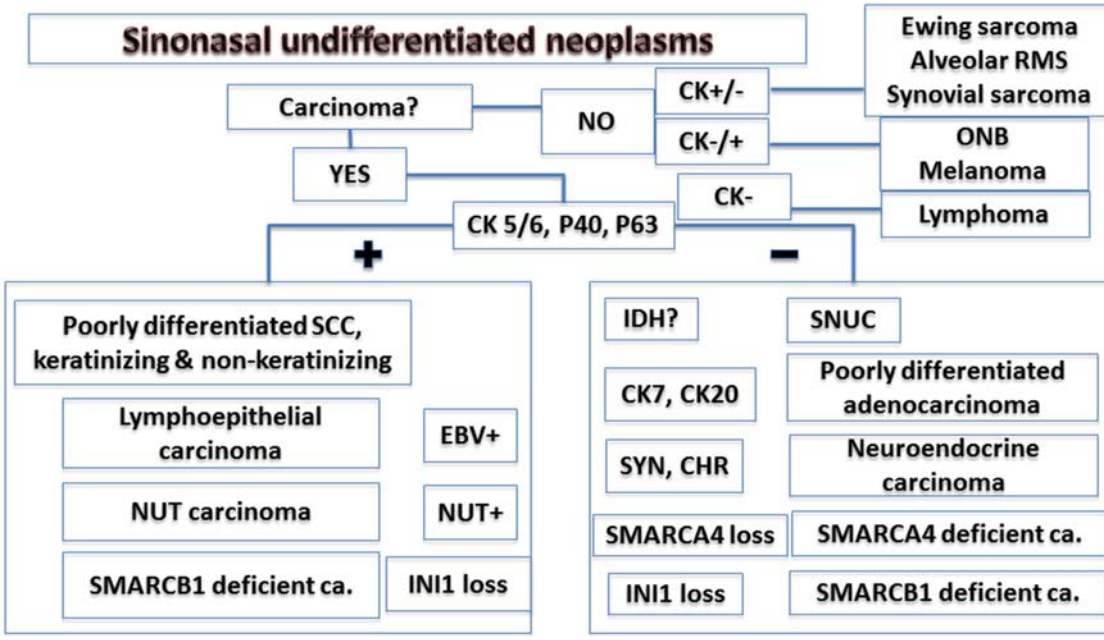

FIGURE 5. An algorithm for the differential diagnostic workup of poorly differentiated sinonasal carcinomas and SNUC. EBV indicates Epstein-Barr virus; IDH, isocitrate dehydrogenase; ONB, olfactory neuroblastoma; RMS, rhabdomyosarcomas; SCC, squamous cell carcinoma; SNUC, sinonasal undifferentiated carcinoma. Please see this image in color online.

characterized by morphology, immunophenotype, and genotype (*IDH* mutations)?

As regards the first and second questions, it is generally accepted that the presence of regularly occurring genotypes such as NUT rearrangements and SWI/SNF-deficiency represents defining genetic events of distinct neoplastic entities irrespective of the organ of origin. Hence, there is no reason to consider the sinonasal tract as an exception. Moreover, the presence of antigenicity subgroups within the SNUC category was already pointed out in the original report.[1] These findings argue against lumping all these *variants* into a morphologically vaguely-defined SNUC category. Recognizing these specific genetic events in undifferentiated neoplasms may be associated with either enhanced radiochemosensitivity or increased response to novel therapies.[49] Accordingly, it seems appropriate to precisely subtype the undifferentiated sinonasal carcinomas to achieve an appropriate definition of their clinicopathologic, biological, and therapeutic properties.

The answer to the third and fourth question is that SNUC seems to represent a distinctive clinicopathologic and genetic entity usually driven by activating *IDH2* mutations, in accordance with the seminal description of this neoplasm as different from other anaplastic sinonasal carcinomas.[1] To this end, the generous use of IDH immunostaining or, if available, mutation testing, is advocated for reliable and reproducible subcategorization of these tumor types. In turn, this would enable further study of those cases qualifying as SNUC but lacking *IDH* mutations. For such cases, the descriptive term "poorly differentiated carcinoma of no special type" might be more appropriate to avoid artificial grouping.

In summary, a minimum set of markers is necessary for the workup of those highly aggressive sinonasal malignancies in the morphologic differential diagnosis of SNUC aiming at the following: (1) exclusion of nonepithelial neoplasms that may occasionally show aberrant expression of simple cytokeratins (such as melanoma, lymphoma, sarcoma); (2) exclusion of specific etiologies such as HPV-related and EBV-associated carcinomas; and (3) identifying and separating genetically defined entities mimicking SNUC, such as NUT carcinoma and *SWI/SNF*-deficient carcinoma (Fig. 5).

Sinonasal Undifferentiated Carcinoma as an IDH-mutant Entity

Within the spectrum of the continuously refining SNUC basket, one is left with tumors that cannot be classified otherwise except as SNUC (Fig. 1). This group of "genuine SNUC" harbors a surprisingly high rate of *IDH2* mutations, approaching 82%. Some authors regard *IDH2*-mutant and *IDH2* wild-type SNUCs as morphologically similar.[41] However, studying the illustrations provided by these authors reveals striking similarities between the *IDH2* mutants and the original SNUC publication.[1,41] In addition, *IDH2* wild-type tumors are remarkably basophilic with small blue cell–like morphology are more akin to tumors in the NUT-rearranged and *SWI/SNF*-deficient groups. Recent studies favor the original description of SNUC as a distinctive entity different from other mimics and usually harboring activating *IDH2* mutations. In contrast to the *SMARCB1* inactivation and the presence of NUT fusion oncoproteins that are known to suppress cell differentiation and hence are associated definitionally with undifferentiated morphology, it is not clear why oncogenic *IDH* mutations in SNUC are associated with undifferentiated phenotype. This contrasts with other *IDH*-mutated, differentiated tumors such as chondrosarcoma, cholangiocarcinoma, gliomas, and others.[43] In conclusion, the available evidence allows

redefining SNUC as an "undifferentiated" sinonasal malignancy that has the following characteristics:

(1) Displays epithelial differentiation but lacks specific squamous, glandular, neuroectodermal, mesenchymal, melanocytic, or other lines of differentiation.
(2) Lacks specific viral etiologies such as HPV and EBV.
(3) Lacks other specific genotypes such as *NUT* fusions, SWI/SNF deficiency, and others.
(4) Lacks genuine neuroendocrine differentiation that would otherwise justify a diagnosis of large cell neuroendocrine carcinoma.
(5) Displays oncogenic *IDH* mutations.

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