Sinonasal Tumors With Neuroepithelial Differentiation (Olfactory Carcinoma)

Delineation of Their Pathologic and Clinical Features With Insights into Their Relationship to Olfactory Neuroblastoma and Sinonasal Carcinoma

Lisa M. Rooper, MD,† Justin A. Bishop, MD,‡ William C. Faquin, MD, PhD,§ Robert D. Foss, DDS,‖¶ Gary L. Gallia, MD, PhD,†#** Vickie Y. Jo, MD,†† James S. Lewis Jr, MD,‡‡§§ Michiya Nishino, MD, PhD,‖‖ Edward B. Stelow, MD,¶¶ Lester D.R. Thompson, MD,## Bruce M. Wenig, MD,*** and William H. Westra, MD†††*

Abstract: Olfactory carcinoma is one of many names applied to sinonasal malignancies with histologic similarity to olfactory neuroblastoma (ONB) but cytokeratin expression or gland formation. It is unclear whether these neuroepithelial tumors represent a unified category and if they are separate from ONB and currently-recognized sinonasal carcinomas. This study aims to explore their clinicopathologic characteristics based on a large collective experience. A total of 53 sinonasal tumors with neuroepithelial differentiation were identified affecting 41 men and 12 women, median age 47 years (range: 12 to 82 y). The vast majority arose in the superior nasal cavity and presented at the high Kadish-Morita stage. Frequent histologic findings included (1) lobulated and solid growth, (2) rosettes and/or neurofibrillary stroma, (3) high-grade cytology, (4) complex, often ciliated glands, (5) nonfocal pancytokeratin expression, (6) neuroendocrine pos +itivity, and (7) variable S100-positive sustentacular cells. Twelve patients with available follow-up (48%) developed progressive disease at a median 8 months (range: 0 to 114 mo to progression), and 7 (28%) died of disease. Despite disparate historical terminology, neuroepithelial differentiation is a recurrent and recognizable histologic pattern that is associated with aggressive behavior in sinonasal tumors. While tumors with this phenotype may originate from olfactory mucosa, well-developed epithelial features warrant separation from conventional ONB and neural elements distinguish them from most sinonasal carcinomas. Although their full histogenesis remains uncertain and some heterogeneity may exist, we propose that this pattern is sufficiently distinctive to merit separate recognition as olfactory carcinoma. Use of consistent nomenclature may facilitate greater recognition of tumors with this phenotype and understanding of their pathogenesis and classification.

Key Words: nasal neoplasms, olfactory neuroblastoma, olfactory carcinoma, neuroendocrine carcinoma, adenocarcinoma, teratocarcinosarcoma, immunohistochemistry

(*Am J Surg Pathol* 2022;00:000–000)

From the Departments of *Pathology; †Oncology; ‖Dermatology; **Otolaryngology—Head and Neck Surgery; #Neurosurgery, The Johns Hopkins University School of Medicine, Baltimore, MD; ‡Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX; §Department of Pathology, Massachusetts General Hospital and Harvard Medical School; ††Department of Pathology, Brigham and Women's Hospital and Harvard Medical School; ‖‖Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA; ¶Head & Neck Pathology, Joint Pathology Center, Silver Spring, MD; Departments of ‡‡Pathology, Microbiology, and Immunology; §§Otolaryngology—Head and Neck Surgery, Vanderbilt University Medical Center, Nashville, TN; ¶¶Department of Pathology, University of Virginia, Charlottesville, VA; ##Head and Neck Pathology Consultations, Woodland Hills, CA; ***Department of Pathology, Moffitt Cancer Center, Tampa, FL; and †††Department of Pathology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY.

W.H.W. is co-corresponding author.

A portion of this data was presented in abstract form at the 2020 USCAP Annual Meeting in Los Angeles, CA.

Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Correspondence: Lisa M. Rooper, MD, The Johns Hopkins Medical Institutions, 401 North Broadway, Weinberg 2242, Baltimore, MD 21231 (e-mail: rooper@jhmi.edu).

Across anatomic sites, neuroendocrine neoplasms are customarily divided into separate categories based on epithelial or neural differentiation. In the sinonasal tract, 3 specific high-grade malignancies are defined along these lines, with small cell neuroendocrine carcinoma and large cell neuroendocrine carcinoma regarded as epithelial neoplasms, and olfactory neuroblastoma (ONB) thought to be of neural lineage.[1–3] While these entities are straightforward to distinguish in their most classic forms, this simplistic taxonomy belies broader ambiguities across the sinonasal neuroendocrine spectrum. Not only do a significant subset of sinonasal tumors with neuroendocrine differentiation display equivocal histologic features and immunoprofiles that preclude assignment to one of these discrete categories[4–7] but contradictory historical literature on the degree of cytokeratin positivity acceptable in ONB and neuroendocrine differentiation allowable in other high-grade sinonasal malignancies has blurred the diagnostic boundaries themselves.[8–16] Recent

recognition of common molecular drivers in phenotypically diverse sinonasal tumors, including *IDH2* mutations in both large cell neuroendocrine carcinoma and sinonasal undifferentiated carcinoma[17–20] and *SMARCA4* inactivation in a group of carcinomas with neuroendocrine features as well as teratocarcinosarcoma,[21–23] has begun to explain some of this overlap and clarify the classification of malignancies with neuroendocrine differentiation. However, many nuances of this differential diagnosis remain poorly understood.

One particularly perplexing phenomenon is a group of sinonasal neuroendocrine tumors that defy the traditional epithelial/neural dichotomy by showing neuroepithelial differentiation, including histologic similarities to ONB suggestive of olfactory neuronal derivation, but with clear-cut epithelial features in the form of cytokeratin positivity or gland formation. The name olfactory carcinoma has previously been proposed for such tumors to reflect their overlapping neuroepithelial elements.[24,25] However, the lack of any meaningful consensus regarding the nature of these tumors is reflected in a plethora of alternative designations, including ONB with divergent epithelial differentiation,[13,26–29] mixed ONB and carcinoma,[30–33] olfactory neuroepithelioma,[12,34–37] mixed-lineage ONB,[24] and blastomatous variant of high-grade sinonasal adenocarcinoma.[38] This taxonomic hodgepodge is almost entirely informed by isolated case reports or small series. It is currently unclear whether these disparate descriptions reflect a heterogenous amalgamation of rare events or a unified clinicopathologic category—and, if so, if these tumors truly represent ONB with divergent differentiation, another type of sinonasal carcinoma, or an entirely separate entity. Lack of uniformity, in turn, has resulted in confusion regarding clinical behavior and appropriate treatment. By assembling a large number of cases from the collective experience of several expert head and neck pathologists, this study aims to systematically characterize the clinicopathologic features of a large group of sinonasal malignancies that show neuroepithelial differentiation to better understand the pathogenesis and classification of these unusual tumors.

MATERIALS AND METHODS

Case Selection

Sinonasal tumors with overlapping features of ONB and sinonasal carcinoma were identified from the authors' consultation files and surgical pathology archives. For inclusion in this study, tumors were required to demonstrate (1) histologic similarities to ONB, (2) immunohistochemical expression of at least 1 specific neuroendocrine marker including synaptophysin, chromogranin, or INSM1, and (3) epithelial differentiation in the form of either nonfocal ($>10\%$) cytokeratin positivity or overt glandular or squamous elements. Tumors that had diagnostic histologic features of small cell or large cell neuroendocrine carcinoma were excluded, as were tumors with stromal or fetal elements that raised consideration of sinonasal teratocarcinosarcoma. As this study was intended to document the full spectrum of tumors recognized to have a neuroepithelial phenotype, no consensus review was performed to limit inclusion. All available histologic sections were reviewed for all cases, and the morphologic features of all tumors were documented in detail. Any available clinical and follow-up information was documented from the electronic medical record.

Immunohistochemistry

The results of all existing immunohistochemical stains were tabulated for all cases. Although there was some variability between institutions, antibodies used in the majority of cases included AE1/AE3 (clone pck-26; prediluted; Ventana Medical Systems, Tucson, AZ), Cam 5.2 (clone Cam 5.2, prediluted; Ventana Medical Systems), synaptophysin (clone 27G12, prediluted; Leica Biosystems, Buffalo Grove, IL), chromogranin (clone LK2H10, prediluted; Ventana Medical Systems), INSM1 (clone A8, 1:200 dilution; Santa Cruz Biotechnology, Dallas, TX), CD56 (clone 123C3.D5; prediluted; CellMarque, Rocklin, CA), S100 protein (clone 4C4.9, prediluted; Ventana Medical Systems), calretinin (clone SP65, prediluted; Ventana Medical Systems), p63 (clone 4a4, prediluted; BioCare Medical, Pacheco, CA), p40 (clone BC28; 1:100; BioCare Medical), IDH2 (clone MABC1103, 1:50 dilution; MilliporeSigma, Burlington, MA), NUT (clone C52B1, 1:50 dilution; Cell Signaling Technologies Inc., Danvers, MA), SMARCA4 (BRG1) (clone EPNCIR111A, 1:00 dilution; Abcam, Cambridge, MA), and SMARCB1 (INI1) (clone 25/BAF47, 1:00 dilution; BD Pharmingen, San Diego, CA). In most cases, staining was performed using standardized, automated protocols on Ventana BenchMark Ultra autostainers (Ventana Medical Systems) in the presence of appropriate controls, and signals were visualized using the ultraView polymer detection kit (Ventana Medical Systems).

RESULTS

Clinical Presentation

Clinical and demographic information is summarized in Table 1. A total of 53 tumors were identified that met inclusion criteria. Affected patients included 41 men and 12 women with a median age of 47 years (range: 12 to 82 y). Twenty-one patients (40%) were younger than 40 years. Two patients had been treated with radiation to the sinonasal tract for childhood retinoblastoma and medulloblastoma 44 and 14 years, respectively, before presentation with the current sinonasal tumor. Information about presenting symptoms were available for 31 patients, all of whom displayed various sequelae of mass effect or local invasion, including nasal congestion, nasal obstruction, epistaxis, nasal or orbital pain, headache, altered mental status, or new-onset seizures. The vast majority of the tumors were centered in the superior aspect of the nasal cavity ($n=44$; 83%), frequently with cribriform plate involvement, with a small subset centered in the ethmoid sinus ($n=6$; 11%) or sphenoid sinus ($n=1$; 2%). The median tumor size was 4.9 cm (range: 1.9 to 9.2 cm). Kadish-Morita stage at presentation was available for 35 patients. Two (6%) had stage A disease confined to the nasal

TABLE 1. Clinical and Demographic Information

Sex	
Male	41 (77)
Female	12 (23)
Age (y)	
Median	47
Range	12-82
Tumor location	
Nasal cavity	44 (83)
Ethmoid sinus	6 (11)
Sphenoid sinus	1 (2)
Unspecified sinonasal	2 (4)
Size	
Median	4.9
Range	1.9-9.2
Kadish-Morita stage	
A	2 (6)
B	13 (37)
C	18 (51)
D	2 (6)
Treatment	
Surgery	23 (92)
External beam radiation	23 (92)
Chemotherapy	14 (56)
Clinical course	
Persistent local disease	3 (12)
Local recurrence	7 (28)
Lymph node metastasis	5 (20)
Distant metastasis	5 (20)
Last known status	
No evidence of disease	15 (60)
Alive with disease	3 (12)
Dead of disease	7 (28)

cavity, 13 (37%) had stage B disease with involvement of the paranasal sinuses, 18 (51%) had stage C disease with extension beyond the sinonasal tract, and 2 (6%) had stage D disease with lymph node or distant metastases. Stage C and D tumors frequently extended intracranially.

Original Diagnoses

These neuroepithelial tumors were originally classified using a broad range of terminology. The most common single diagnosis used was olfactory carcinoma, which was applied in 15 cases (28%). There were also 17 cases diagnosed with variable terminology under the ONB umbrella, including 8 cases (15%) called ONB with divergent epithelial differentiation, 7 cases (13%) with topline diagnoses of ONB and comments describing cytokeratin positivity or epithelial differentiation, and 2 cases (4%) called mixed ONB and carcinoma. An additional 10 cases (19%) were diagnosed as blastomatous variant of high-grade sinonasal adenocarcinoma. Finally, 11 cases were signed out descriptively, including 8 cases (15%) called high-grade carcinoma of probable olfactory neuroepithelial origin, 1 case (2%) called high-grade carcinoma with glandular and neuroendocrine features, 1 case (2%) called high-grade carcinoma with neuroendocrine features, and 1 case (2%) called high-grade basaloid tumor with glandular features.

Histologic Findings

All neuroepithelial tumors were centered in the submucosa without evidence of surface epithelial dysplasia. All cases demonstrated histologic features that were at least partially reminiscent of ONB. Tumors generally displayed a dominant neuroendocrine component with lobulated to nested architecture (Fig. 1A), confluent growth that conferred a more solid appearance (Fig. 1B), and variable amounts of highly vascular stroma (Fig. 1C). These areas also showed frequent evidence of overt neural differentiation, with prominent rosette formation (Fig. 1D) in 33 cases (62%) and neurofibrillary stroma (Fig. 1E) in 11 cases (21%); rare cases also had scattered ganglion-like cells with abundant eosinophilic cytoplasm and round nuclei (Fig. 1F). Tumor cells generally displayed a syncytial appearance with scant cytoplasm and indistinct cytoplasmic borders (Fig. 2A) and often showed a streaming pattern of growth (Fig. 2B). Occasional tumors had intermixed areas of peripheral palisading (Fig. 2C) or ribbon-like architecture with a bipolar nuclear distribution (Fig. 2D). While a minority of cases had round to oval nuclei with speckled chromatin and indistinct nucleoli (Fig. 3A), most displayed enlarged, angulated, and hyperchromatic nuclei (Fig. 3B). A subset of tumors showed more prominent nuclear enlargement and pleomorphism, with nuclear molding and prominent cell-cell wrapping (Fig. 3C) as well as markedly elevated mitotic rate with numerous apoptotic bodies (Fig. 3D) and zones of tumor necrosis. According to Hyams grading criteria for conventional ONB, the majority of cases would be grade 3 (n = 26, 52%) or grade 4 (n = 19, 38%).

Histologic evidence of epithelial differentiation was also seen in 35 cases (66%), including 34 (64%) with well-formed glands and 4 (8%) with occasional squamous pearls. The epithelial nature of the remaining tumors was evident via immunohistochemistry alone. The glands generally consisted of large cells with a moderate amount of eosinophilic cytoplasm and variable degrees of mucin production (Fig. 4A). In 17 cases (32%), the surface of the glands displayed terminal bars with prominent cilia formation (Fig. 4B). Even in cases that demonstrated extremely high-grade neuroendocrine components, the glandular elements generally had round to oval nuclei with less pleomorphism and lacked significant mitotic activity or necrosis (Fig. 4C). Although these features raised the possibility that the glands could represent entrapped surface epithelium, they consistently showed some degree of cytologic atypia, complex proliferative architecture, and intimate admixture with the neuroendocrine cells (Fig. 4D), consistent with true tumor constituents. A few cases only demonstrated focal gland formation (Fig. 4E), while in others, it was challenging to distinguish whether luminal spaces represented glands or rosettes (Fig. 4F). Squamous pearls were much less frequently seen and tended to be small with a compact morular appearance (Fig. 5A). They were often closely intermixed with areas of glandular differentiation (Fig. 5B).

Immunohistochemistry

Results of immunohistochemistry are summarized in Table 2. All tumors demonstrated immunohistochemical expression of at least 1 cytokeratin, including AE1/AE3 in

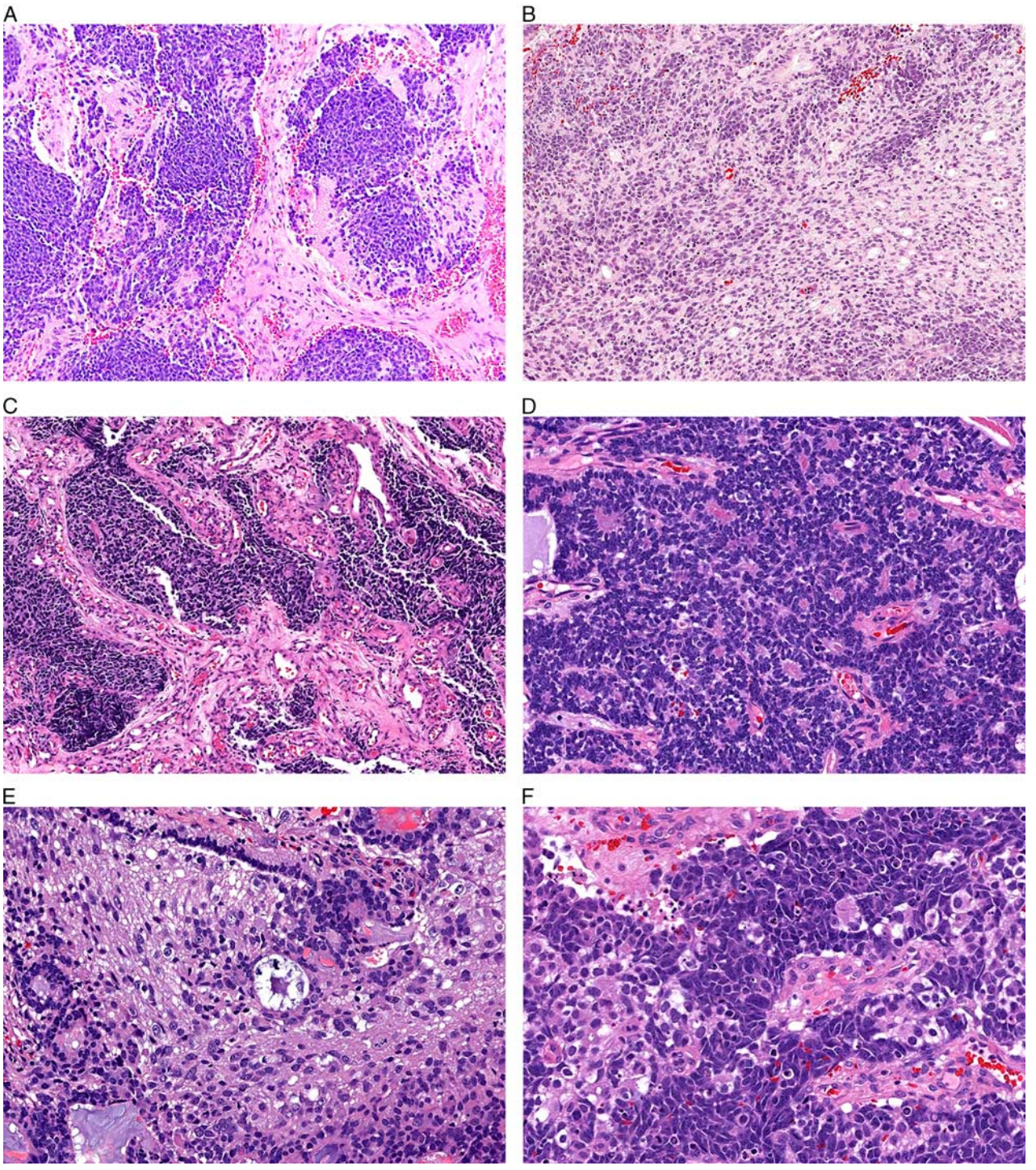

FIGURE 1. Tumors demonstrated notable resemblance to ONB, with lobulated to nested growth (A) that in areas became more confluent and solid (B) and prominent vascular stroma (C). They displayed well-developed neural differentiation, including abundant rosette formation (D), variable amounts of neurofibrillary stroma (E), and occasional ganglion-like cells (F).

51 cases (100%, Fig. 6A) and Cam 5.2 in 24 cases (100%, Fig. 6B). The vast majority of cases displayed nonfocal (positivity in >10% of cells) expression of AE1/AE3, which tended to be stronger in the glands than in neuroendocrine cells, while a few cases showed focal AE1/AE3 but had diffuse Cam 5.2 positivity or prominent glandular elements. The tumors also were positive for at least 1 specific marker of neuroendocrine differentiation, including synaptophysin in 43 cases (86%, Fig. 6C), chromogranin in 25 cases (58%), and INSM1 in 13 cases

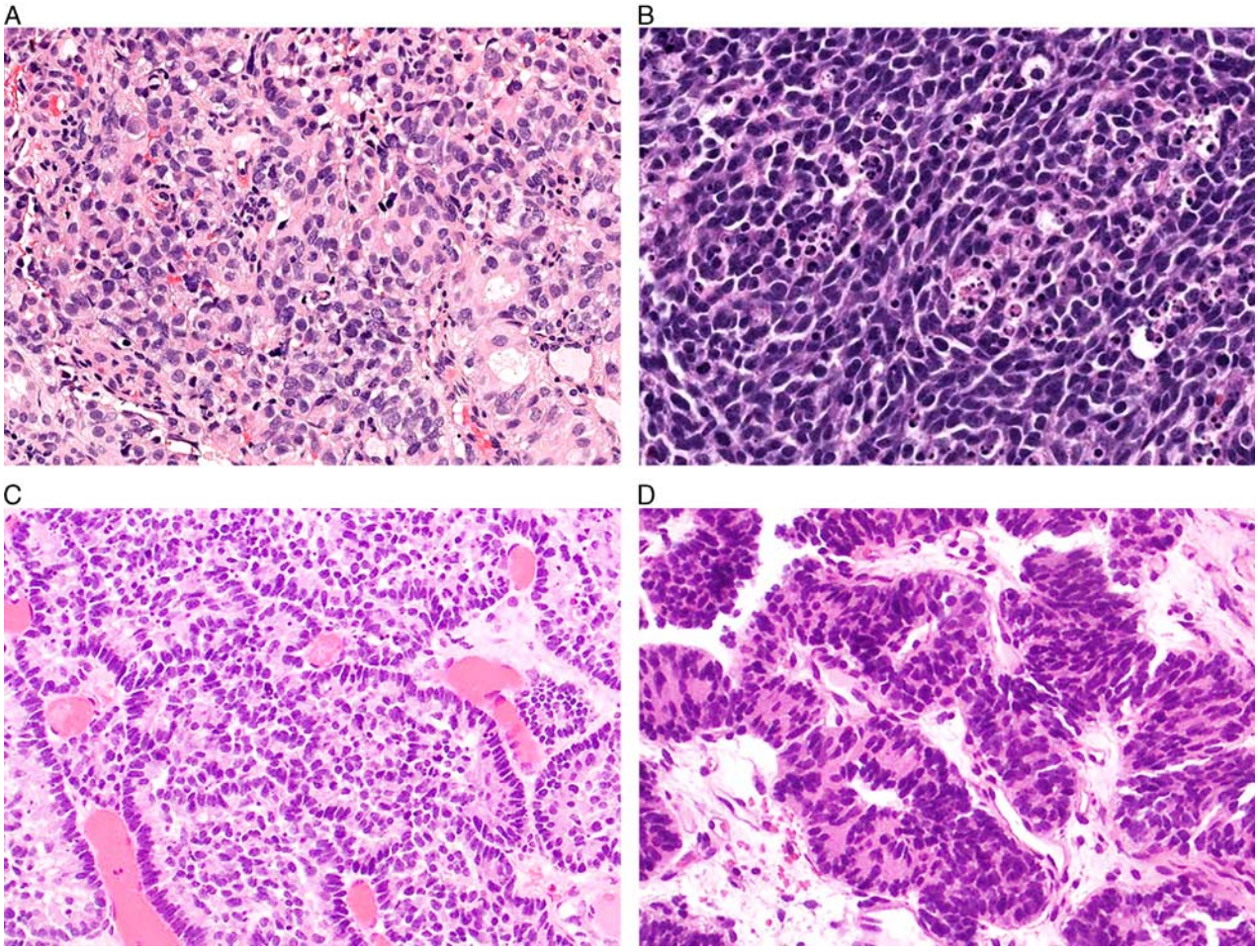

FIGURE 2. Most tumor cells had a syncytial appearance with indistinct cytoplasmic borders (A) and frequently demonstrated a streaming pattern (B). Occasional cases showed peripheral palisading (C) or ribbon-like growth with a bipolar nuclear distribution (D).

(93%, Fig. 6D). Although less specific, CD56 was also positive in 26 cases (93%). In the majority of cases, the intensity of staining of all of the neuroendocrine markers tended to be lower than seen in conventional ONB. Twenty-two cases (51%) displayed at least focal sustentacular S100 protein positivity (Fig. 6E), with occasional concomitant weak expression in tumor cells. There were 6 cases tested (75%) that were positive for calretinin. Patchy p63 or p40 expression was seen in 10 cases tested (37%), frequently with basal accentuation (Fig. 6F). All cases tested were also negative for IDH2 (n = 6) and NUT (n = 12) with intact expression of SMARCA4 (n = 21) and SMARCB1 (n = 18).

Treatment and Follow-up Information

Detailed treatment and follow-up information was available for 25 patients with a median duration of 11 months (range: 2 to 160 mo), as also summarized in Table 1. Most patients were treated with multimodality therapy, including surgery, external beam radiation, and chemotherapy in 12 cases (48%) and surgery and external beam radiation in 8 cases (32%). Notably, 3 patients treated with induction chemotherapy demonstrated dramatic response with minimal residual viable tumor at resection, although 2 of those patients later recurred. There were 12 patients (48%) who developed persistent, recurrent, or metastatic disease at a median interval of 8 months (range: 0 to 114 mo). This included 3 patients (12%) who had persistent local disease after original therapy and 7 patients (28%) who developed local recurrence. Lymph node metastasis were identified in 5 patients (20%), including 1 that was found at presentation. There were also distant metastasis to sites including the lung, spine, chest wall, liver, pancreas, adrenal gland and lacrimal gland in 5 patients (20%), 1 of whom had multifocal metastases at presentation. At the last follow-up, 15 patients (60%) had no evidence of disease, 3 patients (12%) were alive with disease, and 7 patients (28%) had died of disease.

DISCUSSION

Classification of neuroendocrine tumors that arise in the sinonasal tract is plagued by persistent ambiguities.

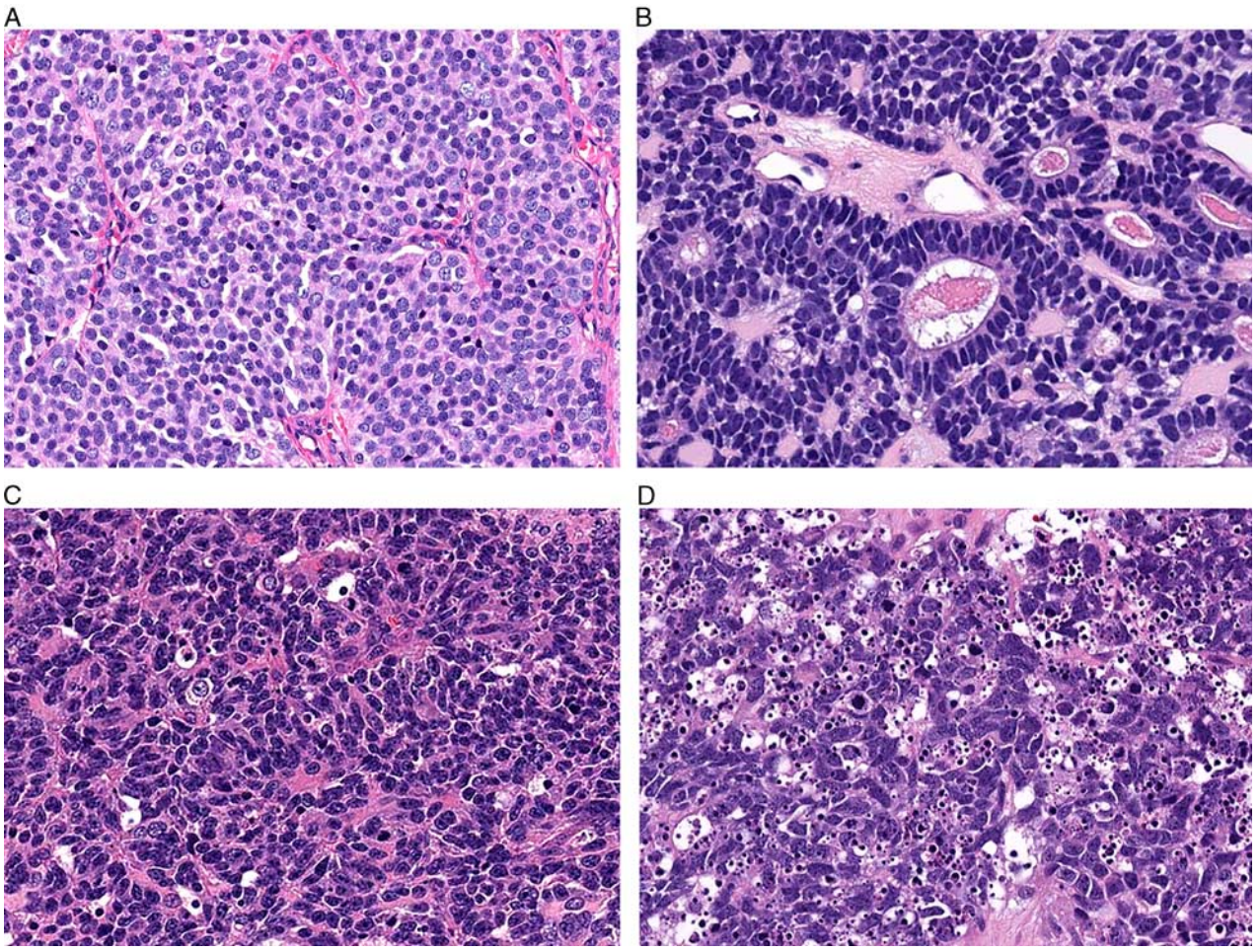

FIGURE 3. While a subset of cases had round to oval nuclei with speckled chromatin (A), most had angulated, and hyperchromatic nuclei (B) with areas of nuclear molding and cell-cell wrapping (C) as well as increased mitoses and abundant apoptotic debris (D).

While molecular reclassification of sinonasal carcinomas has clarified some points in this differential diagnosis, a subset of tumors still remain poorly understood. Particularly problematic is a rare subgroup of malignancies that show hybrid neuroepithelial differentiation, including both neural elements suggestive of ONB as well as clear-cut epithelial features in the form of cytokeratin positivity and/or gland formation. With only limited cases reported in the literature under a wide range of designations, it is unclear whether these overlapping neoplasms represent rare events or a unified group—and, if so, whether they are true ONB with divergent epithelial differentiation, a sinonasal carcinoma with incidental neural elements, or an entirely separate entity. Moreover, the absence of any guiding diagnostic criteria and consensus terminology has handicapped efforts to appraise the pathologic and clinical features of these unusual tumors. In this study, we evaluated the clinicopathologic features of a large cohort of sinonasal neuroepithelial neoplasms to better establish their pathologic features and understand their classification and pathogenesis.

First, our findings highlight a constellation of histologic findings that define a neuroepithelial pattern in sinonasal tumors and suggest that it is a recurrent phenomenon. The majority of cases in this series displayed several key histologic and immunohistochemical characteristics: (1) a mix of nested, lobulated, and solid architecture, (2) overt neural differentiation in the form of rosette formation, neurofibrillary stroma, and occasional ganglion-like cells, (3) cytologically high-grade neuroendocrine cells with enlarged and hyperchromatic nuclei, (4) intermixed complex, often ciliated glands with eosinophilic cytoplasm, (5) nonfocal pancytokeratin expression that is strongest in the glandular component, (6) at least focal positivity for neuroendocrine markers, and (7) variable S100 protein-positive sustentacular cells. Although previous reports of tumors with overlapping features of ONB and epithelial differentiation were described using a diverse range of names,[12,13,24,26–40] rereview of histologic descriptions and photomicrographs of these published cases suggests that most also share similar features to those in our series regardless of original

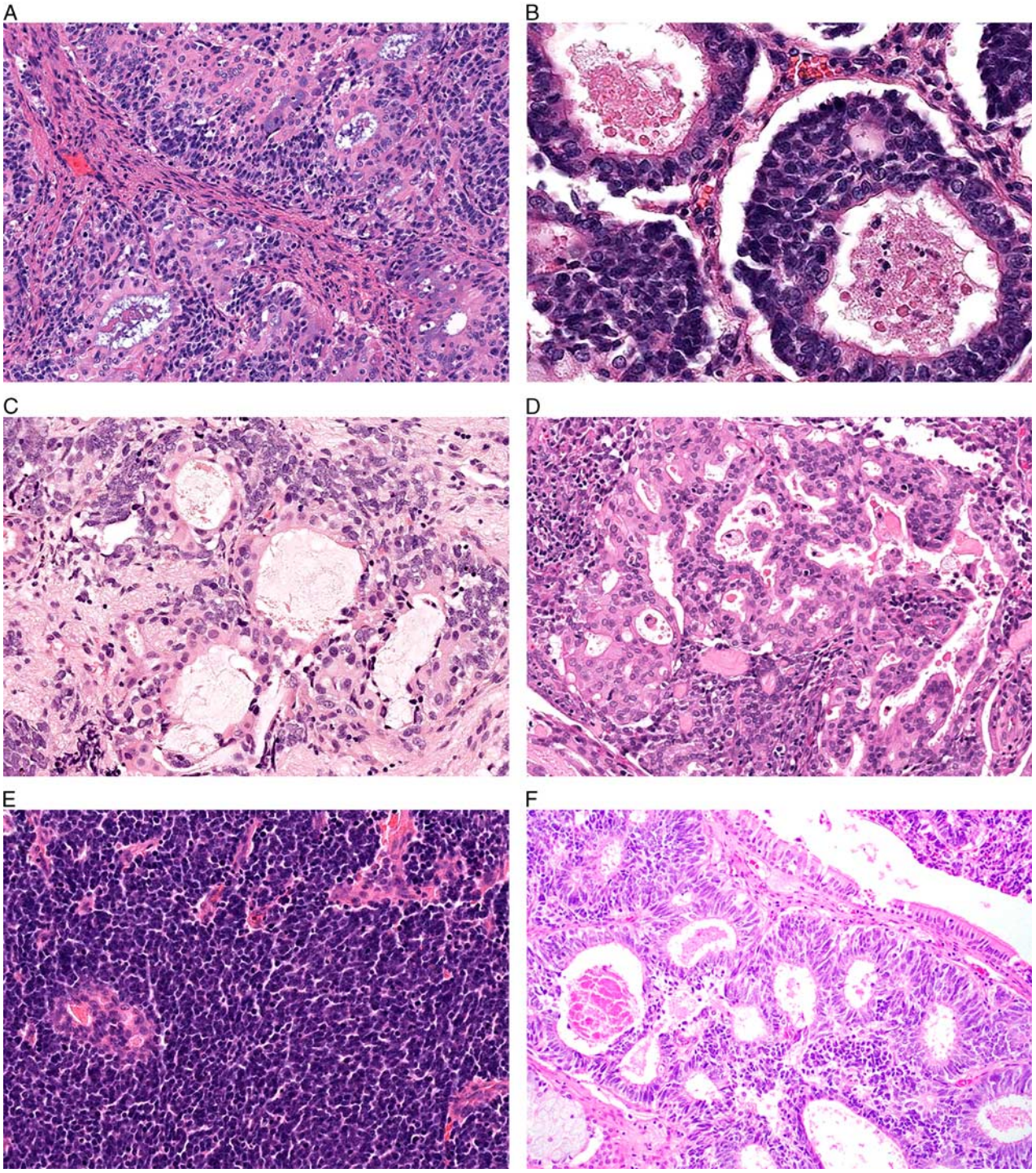

FIGURE 4. A majority of tumors included prominent glands with eosinophilic cytoplasm and variable mucin production (A), often with well-developed cilia (B). These glands had less cytologic atypia than intermixed neuroendocrine cells (C) but showed complex proliferative architecture (D). In a few cases, the glandular component was quite focal (E), while in others, it was difficult to distinguish glands from rosettes (F).

terminology. Importantly, despite these common features, sinonasal neuroepithelial tumors are not entirely uniform across all of these parameters, with a spectrum of overt neural elements, gland formation, cytokeratin expression, and grade in our cohort as well as in previous literature. As such, it is quite likely that these neuroepithelial neoplasms may represent a heterogenous group rather than a single entity. However, these findings suggest that

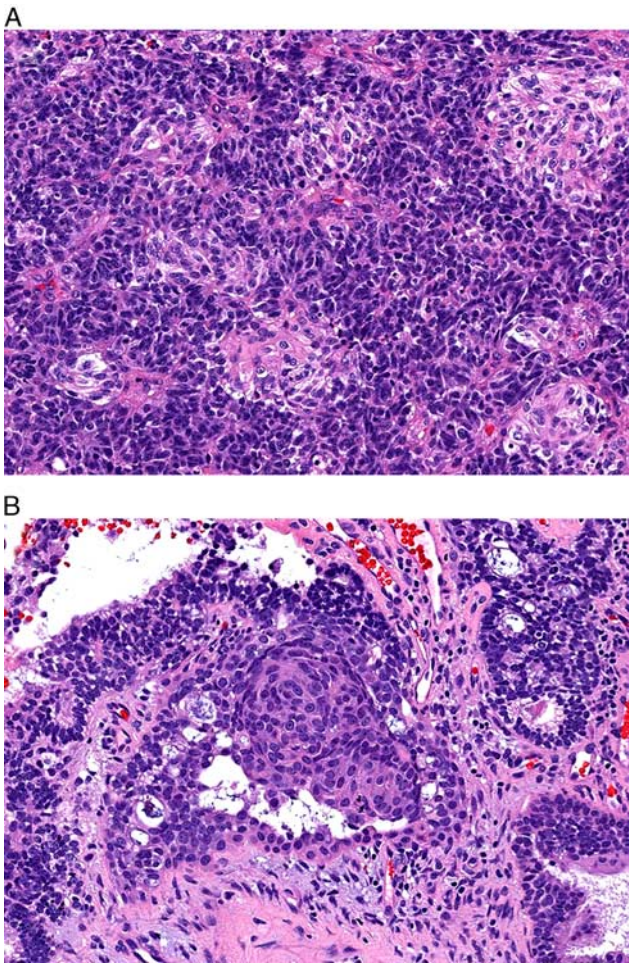

FIGURE 5. Rare cases showed nests of squamous differentiation, which generally had a compact morular pattern (A) and were closely intermixed with glands (B).

neuroepithelial differentiation does comprise a recognizable histologic and immunohistochemical pattern in the sinonasal tract. Moreover, although this phenotype has never been systematically characterized in the literature, the consistent findings across a large number of cases in this series suggest that neuroepithelial differentiation is a recurrent phenomenon worthy of formal recognition rather than a rare aberration.

TABLE 2. Immunohistochemical Results

Stain	No. Positive Cases, n (%)
AE1/AE3	51/51 (100)
Cam 5.2	24/24 (100)
Synaptophysin	43/50 (86)
Chromogranin	25/43 (58)
INSM1	13/14 (93)
CD56	26/28 (93)
S100 (sustentacular)	22/43 (51)
Calretinin	6/8 (75)
p63 or p40	10/27 (37)
IDH2	0/6 (0)
NUT	0/12 (0)
SMARCA4 (intact)	18/18 (100)
SMARCB1 (intact)	21/21 (100)

In addition to distinctive pathologic findings, our results also indicate that sinonasal tumors with neuroepithelial differentiation have characteristic clinical features—most notably a tendency toward aggressive behavior. Although tumors arose across the lifespan, they were most common in young to middle-aged adults, with 40% of cases occurring in patients under 40 years. Men were also disproportionately affected, with a 3.4:1 male: female ratio. Furthermore, these neuroepithelial tumors almost exclusively originated in the superior nasal cavity or ethmoid sinus with frequent involvement of the cribriform plate. Importantly, 57% of tumors demonstrated Kadish-Morita stage C or D disease with extension beyond the sinonasal tract at the time of presentation, including intracranial involvement in many cases. Multimodality therapy, including surgery and external beam radiation in 92% of cases and additional chemotherapy in 56%, was frequently needed to achieve disease control, with a subset of patients showing dramatic response to neoadjuvant chemotherapy. Nevertheless, 48% of patients developed rapidly progressive disease, and, in limited follow-up, 28% died of disease. These clinical characteristics also closely parallel those previously reported in similar tumors under assorted names.[12,13,24,26–40] Of course, this aggressive behavior is not unexpected given the high histologic grade of most of these tumors and by itself does not confirm the presence of a unique category or differentiate these neuroepithelial neoplasms from other high-grade sinonasal tumor types. However, these findings do confirm that these neuroepithelial neoplasms have a recurrent clinical as well as histologic phenotype.

Even with comprehensive documentation of their hybrid clinicopathologic profile, the full relationship of these neuroepithelial neoplasms to ONB remains uncertain. There are undoubtedly strong parallels between these groups of tumors that at least suggest that they have a common cell of origin. By definition, sinonasal tumors with neuroepithelial differentiation show significant overlap with ONB at the morphologic level, including neurofibrillary stroma, S100-positive sustentacular cells, and rosette formations—features traditionally considered specific for an ONB diagnosis. They also show frequent localization to the superior aspect of the nasal cavity, which is lined by the highly specialized olfactory mucosa that also gives rise to ONB. Although olfactory nerve cells and supporting sustentacular cells are histologically and functionally distinct, they are believed to share a common progenitor stem cell—the olfactory basal cell.[41] As such, the epithelial differentiation of neuroepithelial neoplasms may well be within the differentiating potential of the olfactory basal cell in addition to the neural differentiation of ONB, raising the possibility that all of these tumors arise from the same cell type. However, there are also significant differences that seem to warrant a distinction between these neuroepithelial malignancies and ONB. In particular, the degree of cytokeratin positivity seen in sinonasal tumors with neuroepithelial differentiation is not

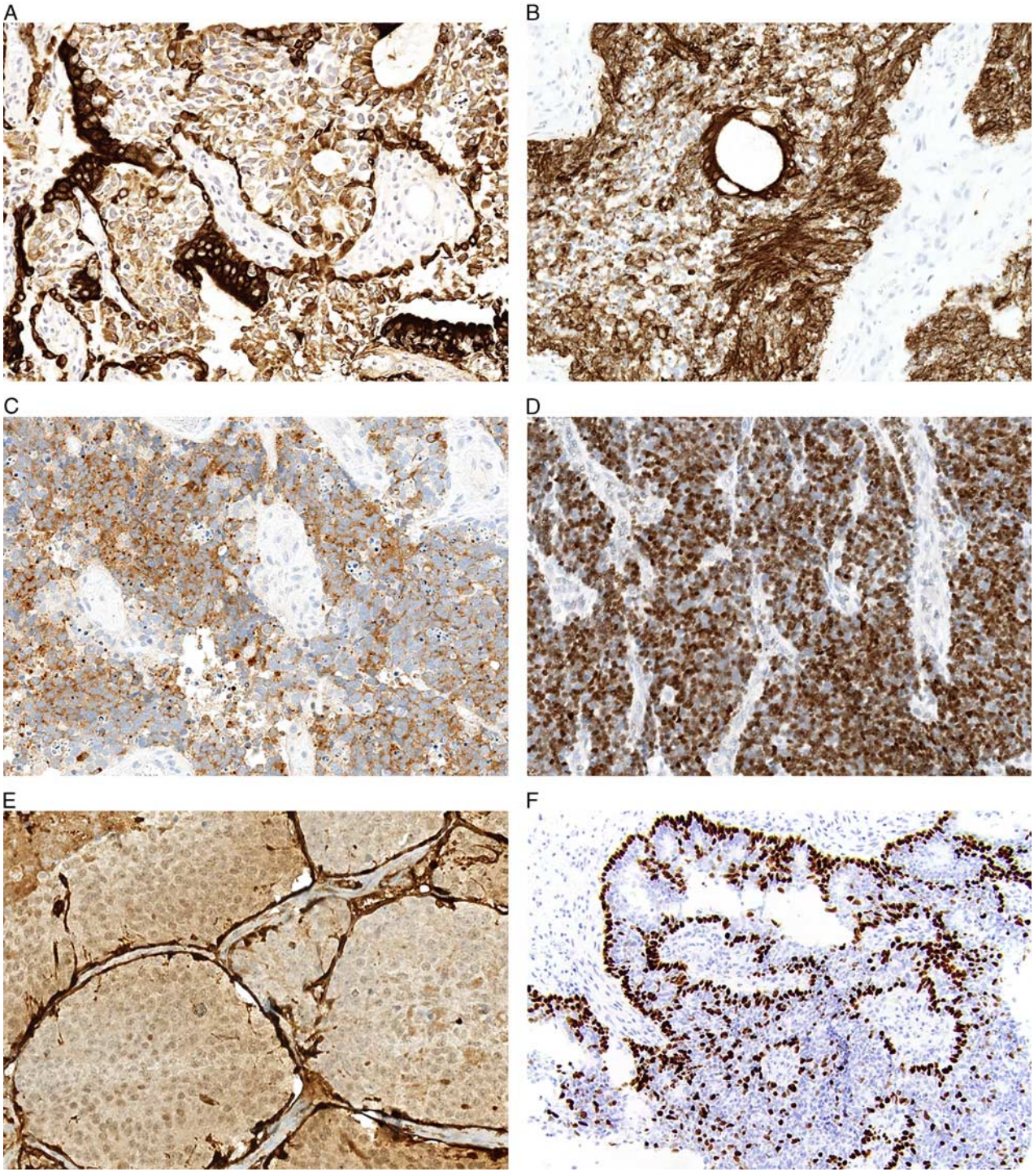

FIGURE 6. Tumors were consistently positive for AE1/AE3 (A) and Cam 5.2 (B), with stronger staining in the glandular than neuroendocrine cells. They also showed consistent but variable expression of specific neuroendocrine markers such as synaptophysin (C) and INSM1 (D). A majority of cases had at least focal sustentacular S100 staining (E), and a subset displayed p63 and p40 in a basal distribution (F).

universally acceptable within current diagnostic boundaries of ONB. While pancytokeratin positivity was historically reported in up to 40% of ONB,[8,10–15] a few of these studies explicitly included the neuroepithelial neoplasms at question here, and it is unclear how other cases would be classified with the benefit of modern immunohistochemistry and molecular genetics. Although this issue remains controversial, 2017 WHO Classification of Head

and Neck Tumours only allows for focal positivity for low molecular weight cytokeratin cocktails such as Cam 5.2 in ONB.[1,6,42] Instead of blurring conventional diagnostic boundaries by accepting extensive gland formation and cytokeratin positivity within the conventional ONB category, we believe it is prudent to recognize those orphan tumors with nonfocal epithelial differentiation as a separate histologic pattern. However, it is still not clear whether this pattern should be considered a variant of ONB or 1 or more separate entities.

Attempts to fit these neuroepithelial malignancies into other established and emerging sinonasal tumor categories are also unsatisfactory. The high-grade cytology, cytokeratin positivity, and expression of neuroendocrine markers seen in these tumors all raise consideration of a high-grade neuroendocrine carcinoma, but overt neural differentiation would be unprecedented in either small cell or large cell neuroendocrine carcinoma.[2,43] Primitive tumors showing glandular and neuroendocrine differentiation have previously been described as blastomatous variant of high-grade sinonasal adenocarcinoma,[38] but true neuroendocrine components are not generally accepted in pure adenocarcinomas at any site and has precluded widespread adoption of this classification. Furthermore, despite reports of other ciliated head and neck malignancies,[44–46] the presence of ciliated cells are relatively unique in the sinonasal tract and have not yet been documented in sinonasal adenocarcinomas. The presence of intermixed neuroepithelial and glandular differentiation is reminiscent of sinonasal teratocarcinosarcoma. However, the neuroepithelial neoplasms in this cohort uniformly lack the additional stromal or fetal elements that define teratocarcinosarcoma, and none of the cases tested demonstrated loss of SMARCA4 expression, which is frequently seen in teratocarcinosarcoma.[23] Interestingly, a subset of sinonasal tumors with *IDH2* mutations have been reported as ONB or ONB-like[17,47,48] and appear to fit within the neuroepithelial spectrum, with lobulated growth and S100-positive sustentacular cells as well as cytokeratin positivity. Although broader evaluation would likely identify more neuroepithelial malignancies with *IDH2* alterations, the few cases in this series screened with IDH2 mutation-specific immunohistochemistry were negative, suggesting that neuroepithelial differentiation is not limited to this category. Overall, while molecular genetic testing may help further define the boundaries of these tumors and align them with the evolving sinonasal tumor classification moving forward, neuroepithelial neoplasms do not perfectly conform to any single existing category at this point.

In summary, this study highlights the existence of a rare but recurrent group of sinonasal malignancies with combined neural and epithelial differentiation that have previously been poorly characterized in the literature. Despite some heterogeneity within this cohort, these findings demonstrate that the majority of these neuroepithelial neoplasms do share a recognizable pathologic profile and frequently display aggressive clinical behavior. However, their classification remains challenging with key similarities and differences to both ONB and other sinonasal tumor types that show neuroendocrine and glandular differentiation. Instead of forcing these tumors into existing categories—and, in doing so, blurring the boundaries of those diagnoses—we propose that these tumors should be separately recognized as a distinctive histologic pattern of uncertain histogenesis. The term olfactory carcinoma, which has prominently been used in previous literature[24,25] and was most commonly applied to them in this coh ort, seems to best reflect the unique histologic, immunohistochemical, and clinical features of tumors with this phenotype. Certainly, additional clinicopathologic and molecular analysis will be necessary to better define the limits of this pattern, evaluate for potential heterogeneity within the group, and determine whether it deserves recognition as 1 or more independent entities or variants of another tumor type. However, consistent use of the olfactory carcinoma designation may allow for greater recognition of sinonasal tumors with a neuroepithelial phenotype and facilitate more complete understanding of their classification, pathogenesis, and treatment.

REFERENCES

1. Bell D, Franchi A, Gillison M, et al. Olfactory neuroblastoma. In: El-Naggar A, Chan JK, Grandis JR, Takata T, Slootweg PJ, eds. *WHO Classification of Head and Neck Tumors*. Lyon, France: International Agency for Research on Cancer; 2017:57–59.
2. Thompson LDR, Bell D, Bishop JA. Neuroendocrine carcinoma. In: El-Naggar A, Chan JK, Grandis JR, Takata T, Slootweg PJ, eds. *WHO Classification of Head and Neck Tumors*. Lyon, France: International Agency for Research on Cancer; 2017:21–23.
3. Franchi A, Wenig BM. Teratocarcinosarcoma. In: El-Naggar A, Chan JK, Grandis JR, Takata T, Slootweg PJ, eds. *WHO Classification of Tumours of Endocrine Organs*. Lyon, France: International Agency for Research on Cancer; 2017:26–27.
4. Turri-Zanoni M, Maragliano R, Battaglia P, et al. The clinicopathological spectrum of olfactory neuroblastoma and sinonasal neuroendocrine neoplasms: Refinements in diagnostic criteria and impact of multimodal treatments on survival. *Oral Oncol*. 2017; 74:21–29.
5. Weinreb I, Perez-Ordonez B. Non-small cell neuroendocrine carcinoma of the sinonasal tract and nasopharynx. Report of 2 cases and review of the literature. *Head Neck Pathol*. 2007;1:21–26.
6. Bell D, Hanna EY, Weber RS, et al. Neuroendocrine neoplasms of the sinonasal region. *Head Neck*. 2016;38(suppl 1):E2259–E2266.
7. Shah K, Perez-Ordonez B. Neuroendocrine neoplasms of the sinonasal tract: neuroendocrine carcinomas and olfactory neuroblastoma. *Head Neck Pathol*. 2016;10:85–94.
8. Frierson HF Jr, Ross GW, Mills SE, et al. Olfactory neuroblastoma. Additional immunohistochemical characterization. *Am J Clin Pathol*. 1990;94:547–553.
9. Malouf GG, Casiraghi O, Deutsch E, et al. Low- and high-grade esthesioneuroblastomas display a distinct natural history and outcome. *Eur J Cancer*. 2013;49:1324–1334.
10. Argani P, Perez-Ordonez B, Xiao H, et al. Olfactory neuroblastoma is not related to the Ewing family of tumors: absence of EWS/FLI1 gene fusion and MIC2 expression. *Am J Surg Pathol*. 1998;22: 391–398.
11. Axe S, Kuhajda FP. Esthesioneuroblastoma. Intermediate filaments, neuroendocrine, and tissue-specific antigens. *Am J Clin Pathol*. 1987; 88:139–145.
12. Fukushima S, Sugita Y, Niino D, et al. Clincopathological analysis of olfactory neuroblastoma. *Brain Tumor Pathol*. 2012;29:207–215.
13. Hirose T, Scheithauer BW, Lopes MB, et al. Olfactory neuroblastoma. An immunohistochemical, ultrastructural, and flow cytometric study. *Cancer*. 1995;76:4–19.
14. Taxy JB, Bharani NK, Mills SE, et al. The spectrum of olfactory neural tumors. A light-microscopic immunohistochemical and ultrastructural analysis. *Am J Surg Pathol*. 1986;10:687–695.

15. Wick MR, Stanley SJ, Swanson PE. Immunohistochemical diagnosis of sinonasal melanoma, carcinoma, and neuroblastoma with monoclonal antibodies HMB-45 and anti-synaptophysin. *Arch Pathol Lab Med*. 1988;112:616–620.
16. Mills SE. Neuroectodermal neoplasms of the head and neck with emphasis on neuroendocrine carcinomas. *Mod Pathol*. 2002;15:264–278.
17. Gloss S, Jurmeister P, Thieme A, et al. IDH2 R172 mutations across poorly differentiated sinonasal tract malignancies: forty molecularly homogenous and histologically variable cases with favorable outcome. *Am J Surg Pathol*. 2021;45:1190–1204.
18. Dogan S, Vasudevaraja V, Xu B, et al. DNA methylation-based classification of sinonasal undifferentiated carcinoma. *Mod Pathol*. 2019;32:1447–1459.
19. Jo VY, Chau NG, Hornick JL, et al. Recurrent IDH2 R172X mutations in sinonasal undifferentiated carcinoma. *Mod Pathol*. 2017;30:650–659.
20. Dogan S, Chute DJ, Xu B, et al. Frequent IDH2 R172 mutations in undifferentiated and poorly-differentiated sinonasal carcinomas. *J Pathol*. 2017;242:400–408.
21. Agaimy A, Jain D, Uddin N, et al. SMARCA4-deficient sinonasal carcinoma: a series of 10 cases expanding the genetic spectrum of SWI/SNF-driven sinonasal malignancies. *Am J Surg Pathol*. 2020;44:703–710.
22. Agaimy A, Weichert W. SMARCA4-deficient sinonasal carcinoma. *Head Neck Pathol*. 2017;11:541–545.
23. Rooper LM, Uddin N, Gagan J, et al. Recurrent loss of SMARCA4 in sinonasal teratocarcinosarcoma. *Am J Surg Pathol*. 2020;44:1331–1339.
24. Seethala RR, Wenig BM, Barnes EL, et al. Olfactory neuroblastoma with divergent differentiation: from ganglioneuroblastoma to carcinoma. *Mod Pathol*. 2007;20:229A.
25. Wenig BM. Olfactory carcinoma. *Atlas of Head and Neck Pathology*. Cambridge, MA: Elsevier; 2015:155–156.
26. Charles NC, Petris CK, Kim ET. Aggressive esthesioneuroblastoma with divergent differentiation: a taxonomic dilemma. *Orbit*. 2016;35:357–359.
27. Meyer C, Hamersley ERS, Manosalva RE, et al. Olfactory neuroblastoma with divergent differentiation: an unusual histologic finding in a rare tumor. *Head Neck Pathol*. 2017;11:531–536.
28. Miura K, Mineta H, Yokota N, et al. Olfactory neuroblastoma with epithelial and endocrine differentiation transformed into ganglioneuroma after chemoradiotherapy. *Pathol Int*. 2001;51:942–947.
29. Shintaku M, Ohta M, Kataoka K, et al. Olfactory neuroblastoma associated with extensive "in situ" lesion and aberrant glandular and rhabdomyosarcomatous differentiation. *Neuropathology*. 2021;41:273–280.
30. Attwood JE, Jeyaretna DS, Sheerin F, et al. Mixed olfactory neuroblastoma and adenocarcinoma with in situ neuroendocrine hyperplasia. *Head Neck Pathol*. 2020;14:792–798.
31. Gandhoke CS, Dewan A, Gupta D, et al. A rare case report of mixed olfactory neuroblastoma: carcinoma with review of literature. *Surg Neurol Int*. 2017;8:83.
32. Miller DC, Goodman ML, Pilch BZ, et al. Mixed olfactory neuroblastoma and carcinoma. A report of two cases. *Cancer*. 1984;54:2019–2028.
33. Lao WP, Thompson JM, Evans L, et al. Mixed olfactory neuroblastoma and neuroendocrine carcinoma: an unusual case report and literature review. *Surg Neurol Int*. 2020;11:97.
34. Hassoun J, Gambarelli D, Grisoli F, et al. Esthesioneuroepithelioma, a true neurosensorial tumor. Light- and electron-microscopic study of a case with endocranial extension. *Acta Neuropathol*. 1981;55:77–80.
35. Sugita Y, Kusano K, Tokunaga O, et al. Olfactory neuroepithelioma: an immunohistochemical and ultrastructural study. *Neuropathology*. 2006;26:400–408.
36. Takahashi H, Ohara S, Yamada M, et al. Esthesioneuroepithelioma: a tumor of true olfactory epithelium origin. An ultrastructural and immunohistochemical study. *Acta Neuropathol*. 1987;75:147–155.
37. Utsuki S, Kawano N, Oka H, et al. Olfactory neuroepithelioma arising from the olfactory placode. *Clin Neuropathol*. 2000;19:7–12.
38. Stelow EB, Mills SE, Jo VY, et al. Adenocarcinoma of the upper aerodigestive tract. *Adv Anat Pathol*. 2010;17:262–269.
39. Chang KC, Jin YT, Chen RM, et al. Mixed olfactory neuroblastoma and craniopharyngioma: an unusual pathological finding. *Histopathology*. 1997;30:378–382.
40. Morita A, Ebersold MJ, Olsen KD, et al. Esthesioneuroblastoma: prognosis and management. *Neurosurgery*. 1993;32:706–714; discussion 714–715.
41. Mills SE. *Histology for Pathologists*. Philadelphia, PA: Lippincott Williams & Wilkins; 2019.
42. Bell D. Sinonasal neuroendocrine neoplasms: current challenges and advances in diagnosis and treatment, with a focus on olfactory neuroblastoma. *Head Neck Pathol*. 2018;12:22–30.
43. Perez-Ordonez B, Caruana SM, Huvos AG, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. *Hum Pathol*. 1998;29:826–832.
44. Bishop JA, Westra WH. Ciliated HPV-related carcinoma: a well-differentiated form of head and neck carcinoma that can be mistaken for a benign cyst. *Am J Surg Pathol*. 2015;39:1591–1595.
45. Bishop JA, Cowan ML, Shum CH, et al. MAML2 rearrangements in variant forms of mucoepidermoid carcinoma: ancillary diagnostic testing for the ciliated and warthin-like variants. *Am J Surg Pathol*. 2018;42:130–136.
46. Radkay-Gonzalez L, Faquin W, McHugh JB, et al. Ciliated adenosquamous carcinoma: expanding the phenotypic diversity of human papillomavirus-associated tumors. *Head Neck Pathol*. 2016;10:167–175.
47. Capper D, Engel NW, Stichel D, et al. DNA methylation-based reclassification of olfactory neuroblastoma. *Acta Neuropathol*. 2018;136:255–271.
48. Classe M, Yao H, Mouawad R, et al. Integrated multi-omic analysis of esthesioneuroblastomas identifies two subgroups linked to cell ontogeny. *Cell Rep*. 2018;25:811.e5–821.e5.