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Research Article

Recurrent Wnt Pathway and *ARID1A* Alterations in Sinonasal Olfactory Carcinoma

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ABSTRACT

Sinonasal tumors with neuroepithelial differentiation, defined by neuroectodermal elements reminiscent of olfactory neuroblastoma (ONB) and epithelial features such as keratin expression or gland formation, are a diagnostically challenging group that has never been formally included in sinonasal tumor classifications. Recently, we documented that most of these neuroepithelial neoplasms have distinctive histologic and immunohistochemical findings and proposed the term "olfactory carcinoma" to describe these tumors. However, the molecular characteristics of olfactory carcinoma have not yet been evaluated. In this study, we performed targeted molecular profiling of 23 sinonasal olfactory carcinomas to further clarify their pathogenesis and classification. All tumors included in this study were composed of high-grade neuroectodermal cells that were positive for pankeratin and at least 1 specific neuroendocrine marker. A significant subset of cases also displayed rosettes and neurofibrillary matrix, intermixed glands with variable cilia, peripheral p63/p40 expression, and S100 protein-positive sustentacular cells. Recurrent oncogenic molecular alterations were identified in 20 tumors, including Wnt pathway alterations affecting *CTNNB1* ($n = 8$) and *PPP2R1A* ($n = 2$), *ARID1A* inactivation ($n = 5$), *RUNX1* mutations ($n = 3$), and *IDH2* hotspot mutations ($n = 2$). Overall, these findings do demonstrate the presence of recurrent molecular alterations in olfactory carcinoma, although this group of tumors does not appear to be defined by any single mutation. Minimal overlap with alterations previously reported in ONB also adds to histologic and immunohistochemical separation between ONB and olfactory carcinoma. Conversely, these molecular findings enhance the overlap between olfactory carcinoma and sinonasal neuroendocrine carcinomas. A small subset of neuroepithelial tumors might better fit into the superseding molecular

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category of *IDH2*-mutant sinonasal carcinoma. At this point, sinonasal neuroendocrine and neuroepithelial tumors may best be regarded as a histologic and molecular spectrum that includes core groups of ONB, olfactory carcinoma, neuroendocrine carcinoma, and *IDH2*-mutant sinonasal carcinoma.

Introduction

Classification of high-grade sinonasal tumors with neuroendocrine differentiation remains one of the most challenging areas of head and neck pathology. Traditionally, this differential diagnosis has been limited to 3 ostensibly discrete entities: olfactory neuroblastoma (ONB), a keratin-negative tumor composed of neuroectodermal cells such as neurofibrillary matrix, rosette formation, and S100 protein-positive sustentacular cells; and small cell and large cell neuroendocrine carcinoma, both keratin-positive epithelial malignancies that share the distinctive morphology of neuroendocrine carcinomas across anatomic sites.[1-5] Increasingly, however, pathologists have recognized a problematic group of sinonasal tumors that genuinely display overlapping features of ONB and neuroendocrine carcinoma, including neuroectodermal elements reminiscent of ONB as well as epithelial differentiation in the form of keratin expression or overt gland formation. Because tumors with this hybrid neuroepithelial phenotype have largely been reported as isolated cases and small series, there is no consensus regarding how they should be classified, with authors variably describing them as ONB with divergent epithelial differentiation,[6-9] mixed ONB and carcinoma,[10-12] olfactory neuroepithelioma,[13-16] blastomatous variant of sinonasal adenocarcinoma,[17] or olfactory carcinoma.[18,19] Consequently, neuroepithelial neoplasms pose persistent difficulties for diagnosis and treatment. Recently, our group compiled a large series of more than 50 sinonasal malignancies with both neuroectodermal elements and epithelial differentiation.[20] We reported that not only did this overlapping neuroepithelial phenotype appear to be a recurrent pattern in sinonasal tumors but also the majority of such neoplasms had specific and recognizable histologic and immunohistochemical features. As such, we proposed that the name olfactory carcinoma best describes the distinctive group of neuroepithelial tumors that have high-grade keratin-positive neuroectodermal cells frequently intermixed with complex, variably ciliated eosinophilic glands. However, the molecular underpinnings of these tumors have not yet been documented. In this study, we performed targeted molecular profiling of a large group of sinonasal olfactory carcinomas in order to better understand their pathogenesis and classification.

Materials and Methods

Case Selection

We identified 23 sinonasal tumors that showed neuroepithelial differentiation as broadly defined in our previous study including (1) histologic similarity to ONB in the form of neuroectodermal cells with scant cytoplasm, lobulated to nested growth, neurofibrillary stroma, and/or S100 protein-positive sustentacular cells and (2) epithelial features as demonstrated by pankeratin positivity in the neuroectodermal cells, with or without overt gland formation.[20] In addition to meeting these histologic criteria, tumors were only selected for inclusion if they had tissue blocks or unstained slides available for molecular testing. The tumors included in the study encompassed 11 cases that were included in our original series and had sufficient tissue available for further analysis as well as 12 cases that were identified subsequently. All available hematoxylin and eosin sections from each case were reviewed by at least 2 expert head and neck pathologists, and the histologic features were tabulated in detail. Any available clinical and follow-up information was gathered from the electronic medical record.

Immunohistochemistry

We tabulated the results of existing immunohistochemistry for all cases. In the majority of cases, antibodies used included AE1/AE3 (clone PCK-26; prediluted; Ventana Medical Systems), Cam 5.2 (clone Cam 5.2; prediluted; Ventana Medical Systems), synaptophysin (clone 27G12; prediluted; Leica Biosystems), chromogranin (clone LK2H10; prediluted; Ventana Medical Systems), INSM1 (clone A8; 1:200 dilution; Santa Cruz Biotechnology), S100 protein (clone 4C4.9; prediluted; Ventana Medical Systems), p63 (clone 4a4; prediluted; BioCare Medical), p40 (clone BC28; 1:100; BioCare Medical), calretinin (clone SP65; prediluted; Ventana Medical Systems), SMARCA4 (clone EPNCIR111A; 1:00 dilution; Abcam), SMARCB1 (clone 25/BAF47; 1:00 dilution; BD Pharmingen), and β-catenin (clone 14; 1:1000; BD Biosciences). Staining for most cases was performed on Ventana BenchMark Ultra autostainers (Ventana Medical Systems) using standardized automated protocols in the presence of appropriate controls, and ultraView polymer detection kits (Ventana Medical Systems) were used to visualize signals. Staining was considered nonfocal if present in $\geq$10% of cells and focal if present in <10% of cells.

Molecular Testing

We performed targeted next-generation sequencing (NGS) on all cases using formalin-fixed paraffin-embedded tissue blocks. Eleven cases underwent NGS at the University of Texas Southwestern Medical Center on a NextSeq 550 (Illumina) using an enriched library containing all exons from >1,425 cancer-related genes created using Custom NimbleGen probes (Roche) as described previously.[21] Five cases underwent NGS at The Johns Hopkins Hospital on the HiSeq 2500 platform (Illumina) with libraries containing the full coding regions of 644 cancer-associated genes created using the SureSelect XT Target Enrichment System (Agilent Technologies), as described in detail elsewhere.[22,23] Five cases underwent NGS at University Hospital Erlangen on a NextSeq 550 using the Illumina TruSight Tumor 170 panel (Illumina) recognizing 170 cancer genes as described previously.[24] One case underwent NGS at the City of Hope Comprehensive Cancer Center on a NextSeq 550 using the Illumina TruSight Oncology 500 panel (Illumina) consisting of DNA sequencing of 523 gene mutations as described elsewhere.[25] One case underwent NGS using the

Table
Clinical and demographic information

Case	Age (y)	Sex	Site	Size (cm)	Treatment	Disease progression	Last status
1	37	M	Nasal	7.7	Surgery/XRT/Chemo	Local recurrence, liver, and spine metastasis at 5 mo	DOD at 6 mo
2	19	M	Nasal	7.3	Surgery/XRT/Chemo	None	NED at 9 mo
3	61	F	Ethmoid	3	Surgery/XRT	None	NED at 160 mo
4	67	F	Nasal	4	Surgery/XRT/Chemo	Local recurrence at 2 mo	DOD at 10 mo
5	47	M	Nasal	6.3	Surgery/XRT	None	NED at 63 mo
6	62	M	Nasal	5.6	Surgery/XRT	None	NED at 10 mo
7	58	F	Nasal	4.8	Surgery/XRT/Chemo	Persistent local disease	DOD at 2 mo
8	28	M	Nasal	NA	Surgery/XRT/Chemo	Local recurrence at 27 mo	AWD at 27 mo
9	82	M	Nasal	NA	NA	NA	NA
10	41	M	Nasal	6.6	NA	NA	NA
11	23	M	Nasal	5.4	XRT/Chemo	Persistent local disease	AWD at 6 mo
12	53	M	Nasal	4.8	Surgery/XRT/Chemo	None	NED at 10 mo
13	76	F	Nasal	NA	NA	NA	NA
14	52	M	Nasal	8	NA	NA	NA
15	32	M	Nasal	NA	NA	NA	NA
16	57	M	Nasal	NA	NA	NA	NA
17	70	M	Ethmoid	2.1	XRT/Chemo	Persistent local disease	AWD at 12 mo
18	74	M	Nasal	4	Surgery/XRT/Chemo	None	NED at 7 mo
19	28	M	Nasal	5.5	Surgery/XRT/Chemo	Local recurrence and mediastinal lymph node metastasis at 12 mo	NED at 30 mo
20	40	F	Nasal	NA	NA	NA	NA
21	56	F	Nasal	NA	NA	NA	NA
22	50	M	Nasal	NA	NA	NA	NA
23	31	F	Nasal	4.9	Surgery/XRT/Chemo	None	NED at 3 mo

AWD, alive with disease; chemo, chemotherapy; DOD, died of disease; NA, not available; NED, no evidence of disease; XRT, external beam radiation.

commercial FoundationOne assay including 324 genes as previously described.[26] The pathogenic relevance of all variants was annotated using the gnomAD, dbSNP, and OncoKB databases.

Results

Clinical and demographic information for all cases is included in Table. The 23 olfactory carcinomas were taken from 16 men and 7 women with a median age of 52 years (range, 19-82 years). The tumors were generally large, with a median size of 5.5 cm (range, 3-8 cm) based on radiographic findings. They uniformly arose near the cribriform plate and olfactory apparatus, including 21 (91%) centered in the superior nasal cavity and 2 (9%) in the ethmoid sinus. They also showed frequent extension into the frontal and maxillary sinuses, nasopharynx, orbital structures, and anterior cranial fossa. Detailed clinical follow-up information was available for 14 patients, of whom all 14 (100%) underwent external beam radiation, 12 (86%) had surgical resection, and 11 (79%) were treated with chemotherapy. Most chemotherapy regimens were small cell protocols including cisplatin and etoposide. After initial therapy, 3 patients (21%) experienced persistent disease and 4 (28%) displayed local recurrence at intervals of 2, 5, 12, and 27 months. In limited available follow-up (median: 10 months), 3 patients (21%) had died of disease, 3 patients (21%) were alive with disease, and 8 patients (57%) were alive with no evidence of disease.

Histologic findings are summarized in Figure 1. In all 23 cases, large excisional biopsy or resection specimens were used for histologic evaluation to avoid sampling error. All tumors were predominantly composed of primitive neuroectodermal cells arranged in irregular lobules and confluent sheets (Fig. 2A) with only occasional compact and rounded nests (Fig. 2B). The intervening stroma showed prominent vascularity. Peripheral nuclear palisading was seen at the interface with the stroma in a subset of cases. A majority of tumors included overt neural elements, including true rosette or pseudorosette formation in 14 cases (70%, Fig. 2C) and production of neurofibrillary matrix in 8 cases (40%) including several tumors that displayed expansile zones of neurofibrillary matrix with rare intermixed ganglion-like cells (Fig. 2D). The neuroectodermal cells showed marked cytologic atypia, with scant, syncytial eosinophilic cytoplasm and large, hyperchromatic nuclei that had coarse chromatin and variably prominent nucleoli and showed frequent nuclear molding and cell-cell wrapping (Fig. 2E). Mitotic figures and apoptotic bodies were abundant, and scattered zones of tumor necrosis were observed (Fig. 2F). Based on the Hyams system for grading ONB, all cases of olfactory carcinoma were grade 3 ($n = 13$, 57%) or grade 4 ($n = 10$, 43%).

Some degree of gland formation was present in 19 cases (83%). While a few cases included expansile, confluent proliferations of back-to-back tubules (Fig. 3A), other cases displayed only scattered single acini (Fig. 3B) or had glands that were intimately intermixed with the neuroectodermal cells throughout the tumor (Fig. 3C). Indeed, a subset of tumors contained areas where it was difficult to distinguish true glands from prominent rosettes (Fig. 3D). The glandular cells were columnar with abundant, dense eosinophilic cytoplasm. Well-formed cilia were present in 13 cases (57%, Fig. 3E), and variable amounts of intracellular and extracellular mucin were evident in several tumors. The glandular cells tended to be of lower grade than the surrounding neuroectodermal cells with monotonous round-to-oval nuclei, homogenous chromatin, and a low mitotic rate (Fig. 3F). Despite the relatively bland cytology of the glands, their complex and irregular architecture and consistent admixture with the neuroectodermal cells throughout the tumor indicated that they were part of the tumor rather than entrapped normal surface epithelium or hamartomatous elements.

Immunohistochemical findings in olfactory carcinoma are also summarized in Figure 1. The neuroectodermal cells in all cases

Figure 1.
The histologic, immunohistochemical, and molecular features of all sinonasal olfactory carcinomas evaluated in this study are summarized, with cases organized by the predominant genetic driver. Only mutations that are predicted to be pathogenic or that involve common cancer genes are depicted in this figure; all alterations including variants of uncertain significance are tabulated in Supplementary Table S1.

showed some degree of pankeratin AE1/AE3 expression, which was nonfocal (>10% of cells staining), albeit frequently weak and patchy, in 20 cases (87%) and focal in 3 cases (13%); staining in the glands was consistently stronger than that in neuroectodermal cells (Fig. 4A). Cam 5.2 also showed nonfocal positivity in 9 cases tested (100%) and was consistently stronger and more diffuse than AE1/AE3. The neuroectodermal cells also expressed at least 1 specific neuroendocrine marker including synaptophysin (Fig. 4B), chromogranin, and INSM1 (Fig. 4D) that ranged in intensity from weak and focal to diffuse and strong. Patchy positivity for p63 or p40 at the basal aspect of the neuroepithelial cells was present in 10 cases tested (52%, Fig. 4E). Although no cases had a diffuse sustentacular network, S100 protein-positive sustentacular cells were at least focally observed in 15 cases tested (65%, Fig. 4E), and calretinin expression was identified in 11 cases tested (85%). Three cases tested (25%) showed nuclear localization of β-catenin (Fig. 4F).

Key molecular findings in olfactory carcinoma are summarized in Figure 1, and full variant information for all cases is tabulated in Supplementary Table S1. Twenty cases (87%) harbored recurrent oncogenic mutations. There were 10 cases (43%) that displayed alterations in genes affecting the Wnt pathway, including *CTNNB1* mutations ($n = 8$), *PPP2R1A* mutations ($n = 2$), and *AMER1* mutation ($n = 1$). Five cases (22%) harbored *ARID1A* inactivation, and 10 cases (43%) demonstrated various other alterations in the SWI/SNF complex, including *SMARCA4* mutations ($n = 7$), *ARID1B* alterations ($n = 4$), and *SMARCB1* mutation ($n = 1$). While the *ARID1A* inactivation was established to be oncogenic and generally occurred in the absence of other definite drivers, the other SWI/SNF alterations were predominantly variants of uncertain significance and frequently accompanied other mutations; they also were not associated with SMARCA4 or SMARCB1 protein loss in all cases tested. A variety of other recurrent pathogenic alterations were also seen, including 2 cases with *IDH2* hotspot mutation (R172S and R172G), 3 cases with *RUNX1* frameshift mutations, 3 cases with inactivating mutations in *CREBBP* or its paralog *EP300*, and 5 cases with diverse *TP53* mutations. Three cases showed nonspecific molecular findings but were histologically identical to

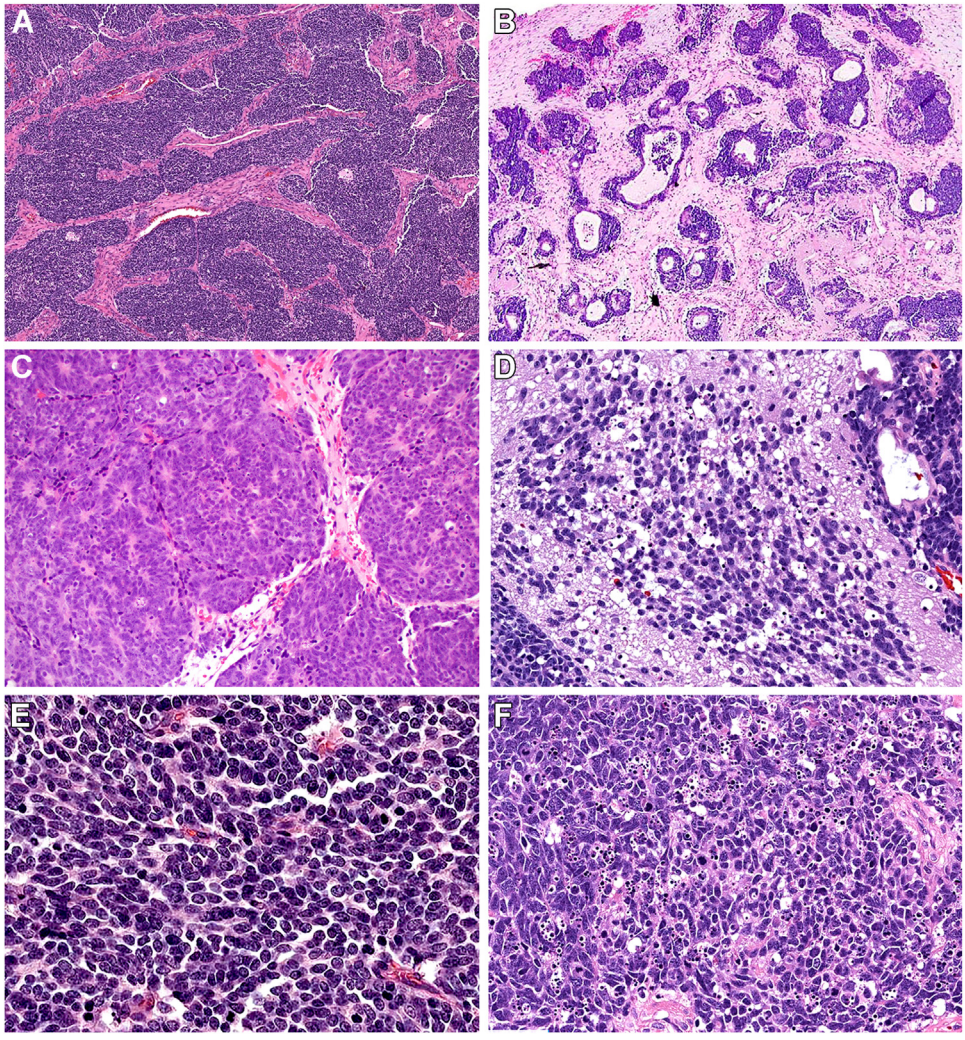

Figure 2.
Olfactory carcinoma was composed of primitive neuroectodermal cells arranged in irregular lobules and sheets (A, 4×) with occasional more compact and rounded nests (B, 4×). The tumor cells frequently formed rosettes and pseudorosettes (C, 10×) and had prominent zones of neurofibrillary stroma (D, 10×). The tumor cells were consistently high grade with hyperchromatic, angulated nuclei that showed prominent molding (E, 20×) and frequent mitotic figures and apoptotic bodies (F, 20×).

the rest of the group. Notably, although both cases with *IDH2* mutation had particularly prominent macronucleoli and compact nested architecture without gland formation, no distinct histologic or immunohistochemical features appeared to be specific for any single genetic alteration.

Discussion

In this study, we demonstrate that the majority of sinonasal olfactory carcinoma have recurrent molecular findings, most notably Wnt pathway and *ARID1A* alterations. Mutations in genes affecting the Wnt pathway, which were seen in 10 cases, comprised the predominant molecular driver in this cohort. These events included not only *CTNNB1* mutations, which are common in many tumor types, but also alterations in *PPP2R1A*, which frequently occur in ovarian and endometrial carcinomas, and *AMER1*, which is rarely reported in colon carcinoma.[27-31] Although only a subset of cases tested had nuclear β-catenin localization, this immunohistochemical finding is known to be variable and tumor type-dependent,[32,33] and all Wnt pathway mutations involved hotspots that previously have been documented to have an oncogenic effect. The other dominant finding was inactivating alterations in *ARID1A*. Inactivating *ARID1A* mutations, which are common in ovarian and endometrial carcinomas,[34] did appear to be the main driver in 5 tumors, all of which lacked Wnt pathway alterations. While alterations in other SWI/SNF chromatin remodeling complex members *SMARCA4*, *ARID1B*, and *SMARCB1* were also seen, the full implication of these mutations was unclear because most alterations were variants of uncertain significance and did not show associated immunohistochemical loss of the respective proteins. As such, although the repeated involvement of these genes suggests that they may play a role in neuroepithelial differentiation, only *ARID1A* appears to be a defining molecular event. Among tumors that lacked Wnt pathway or *ARID1A* mutations, there were 2 other recurrent oncogenic alterations. Two cases displayed *IDH2* hotspot mutations, which are well-established in other high-grade sinonasal tumors as discussed in more detail below. Additionally, 3 cases had pathogenic *RUNX1* frameshift mutations—alterations that are far more common in leukemia but have rarely been implicated in breast carcinoma and other solid tumors.[35,36] Overall, while recurrent

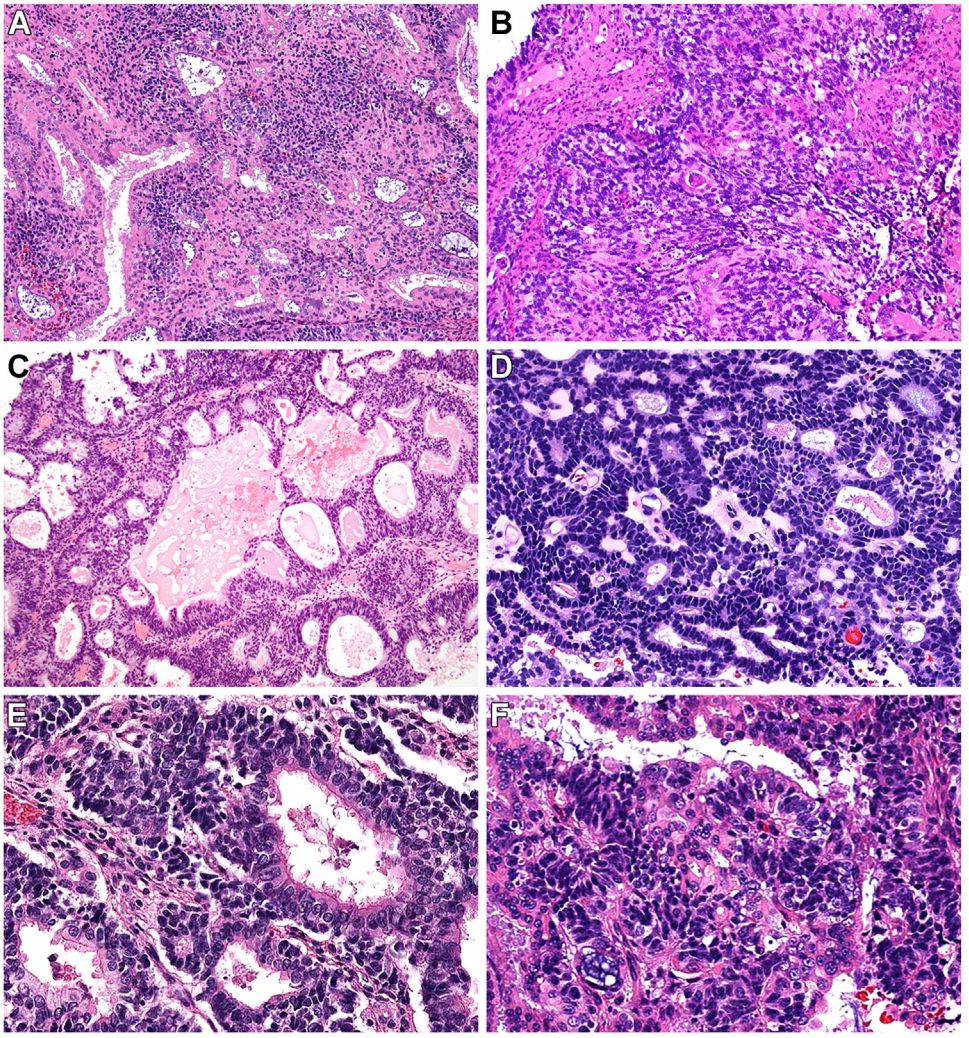

Figure 3.
The vast majority of olfactory carcinoma showed some degree of gland formation, including expansile proliferations of confluent tubules (A, 10×), rare acini surrounded by neuroectodermal cells (B, 10×), or glands intimately intermixed with the neuroepithelial cells throughout (C, 10×). In some cases, the glands were difficult to distinguish from true rosettes (D, 20×). Well-formed cilia were seen in a subset of cases (E, 40×). The glandular cells were lower grade than surrounding neuroectodermal cells and displayed round, regular nuclei (F, 40×).

molecular findings reinforce the distinctive morphologic and immunohistochemical features of olfactory carcinoma, the diversity of implicated alterations suggests that this group of tumors cannot be regarded as a mutation-specific entity.

These results also suggest some separation between olfactory carcinoma and ONB at a molecular level. It is undeniable that there are key similarities between olfactory carcinoma and ONB. Historically, many pathologists have entirely folded neuroepithelial tumors into the ONB category due to their neuroectodermal elements—a feature that was traditionally regarded as unique to ONB in the sinonasal tract. The presence of some degree of epithelial differentiation in otherwise classic ONB, including focal keratin positivity or glandular elements, also blurs the line with olfactory carcinoma.[1,4,37,38] However, olfactory carcinoma generally displays much more extensive keratin expression and gland formation than is regarded as acceptable in ONB, providing a point of histologic and immunohistochemical differentiation.[1-5,20] Now, the presence of Wnt pathway and *ARID1A* mutations in olfactory carcinoma create an additional level of molecular divergence from ONB, which has never demonstrated recurrent oncogenic drivers across multiple studies employing whole exome/genome sequencing or large targeted panels encompassing more than 400 cancer genes (which included *CTNNB1* and *ARID1A*). Instead, a heterogeneous array of somewhat nonspecific alterations including *TP53*, *PIK3CA*, *NF1*, *CDKN2A*, *CDKN2C*, *CCND1*, and *FGFR3* mutations has each been reported in small numbers of ONB.[39-43] Although isolated cases categorized as ONB did have *CTNNB1* or *ARID1A* mutations,[39,41-43] histologic and immunohistochemical details of these tumors are not available, and we strongly suspect that they would be classified as olfactory carcinoma using the above criteria. Other studies with central pathology review that applied strict requirements for keratin negativity in ONB found no evidence of these alterations.[40] Certainly, ONB and olfactory carcinomas share enough features to support some relationship between these groups, and additional molecular comparison is needed to parse out this overlap using current histologic criteria. However, in combination with morphologic and immunohistochemical distinctions, the presence of unique and recurrent driver mutations suggests that olfactory carcinoma should not be fully subsumed within the ONB category.

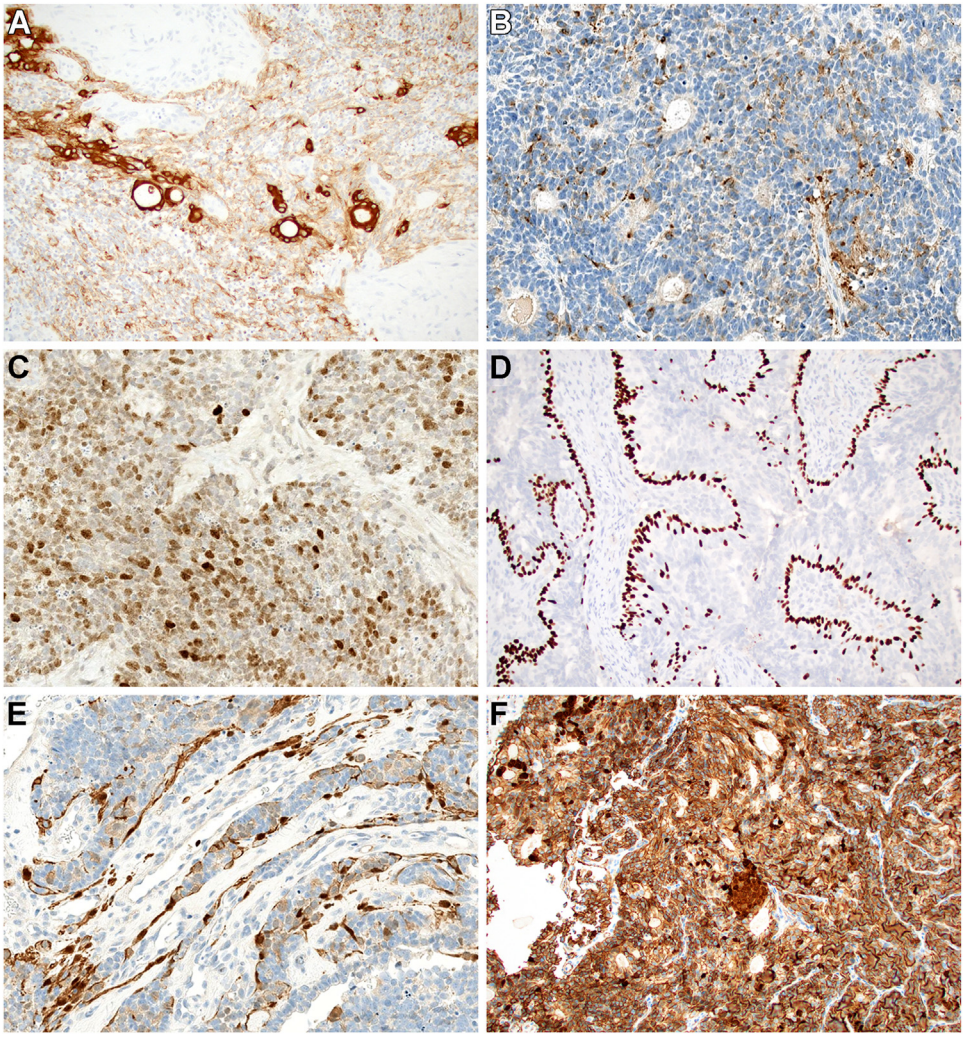

Figure 4.
The olfactory carcinomas showed consistent AE1/AE3 expression that ranged from weak and patchy in the neuroectodermal cells to strong in the glandular cells (A, 10×). The neuroectodermal cells also showed variable expression of neuroendocrine markers including synaptophysin (B, 20×) and INSM1 (C, 20×). More than half of the cases displayed patchy positivity for p63 or p40 at the basal aspect of the neuroepithelial nests (D, 10×) and sustentacular positivity for S100 protein (E, 10×). Focal nuclear β-catenin positivity was present only in rare cases (E, 20×).

The molecular profile of olfactory carcinoma also raises the possibility that sinonasal neuroepithelial tumors may be on a spectrum with sinonasal neuroendocrine carcinomas and sinonasal teratocarcinosarcoma (TCS). Histologically, there is substantial overlap between the keratin-positive neuroectodermal elements of olfactory carcinoma and small cell and large cell neuroendocrine carcinoma. Indeed, in the absence of overt neural differentiation or intermixed glands, the high-grade cells in these tumors are essentially indistinguishable. There is also increasing evidence of molecular similarities between these groups, with Dogan et al[44] reporting that many sinonasal neuroendocrine carcinomas have *ARID1A* or Wnt pathway mutations that closely parallel the findings seen here in olfactory carcinoma. This histologic and molecular resemblance suggests that many sinonasal neuroendocrine carcinomas may be closely related to neuroepithelial neoplasms. Olfactory carcinoma also shares some broad histologic and molecular parallels with sinonasal TCS, although these diagnoses appear less closely aligned. While both tumors are multilineage malignancies with primitive neuroectodermal components, olfactory carcinoma lacks the mesenchymal elements and fetal-like elements (eg, clear squamous cells) diagnostic of TCS. Similarly, although both tumors have Wnt pathway and SWI/SNF complex alterations, most TCS display biallelic-inactivating *SMARCA4* mutations with concomitant loss of protein expression that are not seen in olfactory carcinoma.[45,46] Interestingly, Jurmeister et al[47] recently reported *ARID1A*, *CTNNB1*, and *SMARCA4* mutations in a group of sinonasal neuroendocrine tumors that showed a common methylation profile distinct from that of ONB and *IDH2*-mutant sinonasal carcinomas, although detailed histologic description was not provided. Although further investigation of the relationship between all these categories is needed in a histologically well-annotated cohort, these commonalities indicate that olfactory carcinoma and neuroendocrine carcinoma may exist on a spectrum.

Finally, the presence of *IDH2* hotspot mutations in 2 cases confirms that a subset of sinonasal neuroepithelial tumors fit into the emerging category of *IDH2*-mutant sinonasal carcinoma. *IDH2* R172X mutations were initially identified as the dominant molecular event in tumors still categorized as sinonasal undifferentiated carcinoma after reclassification of multiple molecularly

defined entities.[48,49] They were subsequently reported in the majority of sinonasal large cell neuroendocrine carcinomas.[44] Some controversy has emerged regarding the presence of *IDH2* mutations in ONB. While initial studies proposed that *IDH2* mutations defined a unique group of keratin-positive ONB,[39,50] a subsequent consensus review suggested that many of these tumors are better classified as large cell neuroendocrine carcinoma.[51] Nevertheless, a few cases of *IDH2*-mutant tumors have been reported that show unequivocal neuroectodermal elements, including neurofibrillary stroma, rosette formation, and S100 protein-positive sustentacular cells despite keratin positivity.[51] In this study, we identified 2 additional such cases that had *IDH2* R172X mutations and met criteria for olfactory carcinoma. Notably, although these 2 cases both lacked gland formation and did demonstrate the prominent nucleoli and nested architecture previously described in other *IDH2*-mutant sinonasal tumors,[51] they were otherwise similar to all other neuroepithelial tumors in this series. At this point, olfactory carcinoma could be regarded as a third high-grade sinonasal tumor type that can harbor *IDH2* mutations. However, Gloss et al[51] recently proposed that *IDH2*-mutant sinonasal carcinomas should be recognized as a single molecularly defined entity, regardless of morphologic features because of their common clinical outcomes and methylation profiles[51]—a strategy that might overcome the diagnostic difficulties posed by their variable undifferentiated, large cell neuroendocrine or neuroepithelial phenotypes. Under this classification, the presence of *IDH2* hotspot mutations would supersede the diagnosis of olfactory carcinoma despite overlapping histologic features.

In summary, this study demonstrates that the vast majority of sinonasal olfactory carcinoma show recurrent molecular alterations including frequent Wnt pathway and *ARID1A* mutations. Despite common neuroectodermal features, these molecular findings do support some separation of olfactory carcinoma from conventional ONB, which largely lacks these alterations. Additionally, these results suggest that olfactory carcinoma may be related to sinonasal neuroendocrine carcinoma, which harbors similar genetic underpinnings. The histologically defined group of olfactory carcinoma also includes occasional cases with *IDH2* mutations that might better be included in the emerging molecularly defined category of *IDH2*-mutant sinonasal carcinoma. Given multiple levels of morphologic, immunohistochemical, and molecular overlap, at this point, it may be most prudent to regard sinonasal neuroendocrine and neuroepithelial neoplasms as a spectrum that includes core groups of ONB, olfactory carcinoma, neuroendocrine carcinoma, and *IDH2*-mutant sinonasal carcinoma. While there are still nuances in classification that need to be further explored and resolved at the boundaries of these diagnoses, acknowledgment of olfactory carcinoma as a distinctive group of neuroepithelial tumors within this sinonasal neuroendocrine and neuroepithelial spectrum may allow for more consistent classification and understanding of these unique neoplasms in the future.

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In many discussions over the years, Dr Dennis Knight Heffner (1938 to 2022, Armed Forces Institute of Pathology, Chairman of Otorhinolaryngic-Head and Neck and Endocrine Pathology Department) strongly advocated for the classification of olfactory carcinoma, a diagnosis he rendered regularly accompanied by a very long explanatory note! His colleagues (L.D.R.T. and B.M.W.) gratefully appreciate his mentorship and insight into this group of tumors.

Author Contributions

L.M.R. and J.A.B. designed the study and prepared the manuscript; L.M.R., J.A.B., A.A., D.B., G.L.G., V.Y.J., J.S.L., N.R.L., M.N., L.D.R.T., N.U.D., B.M.W., and W.H.W. contributed to tumor samples and data analysis; and J.G. and R.S. analyzed the sequencing data and interpreted the results. All authors read and approved the final paper.

Data Availability

The data sets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Declaration of Competing Interest

N.R.L. receives funding from Merck and holds stock in Navigen Pharmaceuticals, neither of which is related to the present study. The other authors have no competing interests to declare.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Boards at UT Southwestern Medical Center and Johns Hopkins Medical Institutions.

Supplementary Material

The online version contains supplementary material available at https://doi.org/10.1016/j.modpat.2024.100448

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