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# Recurrent Loss of SMARCA4 in Sinonasal Teratocarcinosarcoma

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**Abstract:** Molecular analysis has reshaped the landscape of high grade sinonasal tumors by defining novel entities and identifying recurrent mutations in established tumor types. However, sinonasal teratocarcinosarcoma (TCS), a rare and aggressive tumor with intermixed teratomatous, carcinomatous, and sarcomatous elements, remains poorly understood. The multiphenotypic differentiation of TCS has engendered persistent controversy about its histogenesis and leads to diagnostic overlap with several other malignancies. In this study, we evaluated the molecular underpinnings of TCS to clarify its pathogenesis and diagnosis. We performed SMARCA4 immunohistochemistry (IHC) on 22 TCS and 153 other sinonasal tumors. We identified loss of SMARCA4 expression in 18 TCS (82%), including 15 (68%) with complete loss and 3 (14%) with partial loss. Although we also identified partial SMARCA4 loss in 1 of 8 SMARCB1-deficient sinonasal carcinomas (13%), SMARCA4 was intact in all other sinonasal carcinomas and neuroendocrine tumors. We then selected 3 TCS with complete SMARCA4 loss by IHC for a targeted next-generation sequencing panel that included 1425 cancer-related genes. We confirmed biallelic somatic inactivation of *SMARCA4* without other known oncogenic mutations in these 3 cases. Overall, these findings suggest that *SMARCA4* inactivation may be the dominant genetic event in TCS, expanding understanding of this gene's role in sinonasal tumorigenesis. They also raise the possibility that TCS is on a diagnostic spectrum with the newly described SMARCA4-deficient sinonasal carcinoma, blurring the lines between established and emerging sinonasal entities. In addition, SMARCA4 IHC may provide a useful adjunct for confirming a diagnosis of TCS in limited material.

**Key Words:** nasal neoplasms, nasal cancers, malignant teratocarcinosarcoma, SMARCA4, BRG1, immunohistochemistry, molecular diagnostics

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## BACKGROUND

Historically, poorly differentiated sinonasal carcinomas have been grouped into broad categories of squamous cell carcinoma, small cell or large cell neuroendocrine carcinoma, and intestinal or nonintestinal adenocarcinoma based on morphologic and immunohistochemical (IHC) features, with tumors that do not fit in other categories designated as sinonasal undifferentiated carcinoma. In the last decade, however, definition of novel entities characterized by specific mutations and recognition of recurrent genetic events in existing tumor types has dramatically reshaped this classification. A significant subset of sinonasal tumors previously categorized as sinonasal undifferentiated carcinoma are now defined by inactivation of *SMARCB1*[1–3] or recurrent *IDH2* mutations,[4,5] primitive tumors with squamous differentiation have been recognized as NUT carcinoma,[6,7] and adamantinoma-like Ewing sarcoma,[8] and a group of high grade tumors with variable neuroendocrine features have been shown to demonstrate *SMARCA4* loss.[9] Moreover, lines have blurred between traditional categories and these novel entities with recent recognition that a subset of nonintestinal adenocarcinomas also shows loss of *SMARCB1*,[10] and tumors with neuroendocrine differentiation can also demonstrate *IDH2* mutations.[11]

Despite this increasingly refined classification, teratocarcinosarcoma (TCS) is one high grade sinonasal tumor that remains particularly poorly understood. As its name suggests, TCS is defined histologically by features of malignant teratoma, carcinoma, and sarcoma, encompassing a characteristic admixture of primitive neuroepithelial tissue, squamous, and glandular epithelium that frequently has a fetal-like clear cell appearance, and a variety of mesenchymal elements.[12] This morphologic heterogeneity can make it difficult to differentiate TCS from a wide range of overlapping entities in small biopsies, particularly when only 1 or 2 components are sampled. It also has precipitated longstanding controversy regarding the



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histogenesis of this tumor type, with theories including true germ cell derivation similar to malignant teratoma, divergent differentiation of a high grade neuroectodermal tumor, and origin from somatic pluripotent stem cells in the olfactory membrane.[13–17] Unlike other sinonasal tract tumors, however, molecular analysis has not yet been widely applied to clarify the pathogenesis of TCS. Although an activating *CTNNB1* mutation has been reported in a single case of TCS that underwent next-generation sequencing (NGS),[18] it is unclear whether this represents a recurrent event or isolated finding. In this study, we sought to further evaluate the molecular underpinnings of TCS to better understand its pathogenesis and classification and to facilitate more specific and reproducible diagnosis, especially on limited biopsy material.

## METHODS

### Case Selection

After institutional review board approval, 22 cases of sinonasal TCS were identified from the surgical pathology archives of The Johns Hopkins Hospital, Aga Khan University Hospital, and the authors' consultation files. Four of these cases (#10-13) had been reported previously.[19] All available slides for each case were re-reviewed for the purposes of this study by at least 2 expert head and neck pathologists (A.A., J.A.B., K.R.M., L.M.R., L.D.R.T., and N. U.), and diagnosis of TCS was confirmed according to World Health Organization criteria including the presence of mixed epithelial, mesenchymal, and primitive neuroepithelial elements.[12] Clinical and demographic data as well as any available treatment and follow-up information was gathered from the electronic medical record. An additional 153 sinonasal carcinomas and neuroendocrine tumors were also selected for evaluation as a comparison group, of which 139 were included on previously constructed tissue microarrays.[6,20]

### Immunohistochemistry

On the basis of results from a pilot case stained as part of an exploratory analysis, IHC for SMARCA4 (1:00 dilution, clone EPNCIR111A; Abcam, Cambridge, MA) was performed on all 22 cases of TCS and 153 additional sinonasal carcinomas and neuroendocrine tumors. All TCS cases with sufficient tumor tissue available also underwent IHC for SMARCB1 (1:00 dilution, clone 25/BAF47; BD Pharmingen, San Diego, CA), SMARCA2 (1:100 dilution, polyclonal; Sigma-Aldrich, St. Louis, MO), and Claudin-4 (1:100 dilution, clone 3E2C1; Thermo Fisher Scientific). Briefly, 4 μm whole-slide or tissue microarray sections were cut from formalin-fixed paraffin-embedded tissue blocks. Antigen retrieval and staining was performed using standardized automated protocols on Ventana BenchMark Ultra autostainers (Ventana Medical Systems, Tucson, AZ) in the presence of appropriate controls, and signals were visualized using the ultraView polymer detection kit (Ventana).

### Next-generation Sequencing

Following IHC, 3 cases of SMARCA4-deficient TCS were submitted for NGS to assess the significance of the IHC loss. Priority was given to recent cases that had abundant tumor tissue to maximize the likelihood of having sufficient well-preserved nucleic acids for sequencing. NGS was performed as previously described.[21] In short, 10 μm sections were cut from formalin-fixed paraffin-embedded tissue blocks, and DNA and RNA were isolated using Qiagen AllPrep kits (Qiagen, Germantown, MD). Custom probes were used to produce an enriched library containing all exons from >1425 cancer-related genes, and sequencing was performed on the NextSeq 550 (Illumina, San Diego, CA) with a median target exon coverage of 900×. Variants were reviewed using the Integrated Genomics Viewer (Broad Institute, Cambridge, MA) and somatic variants were identified on the basis of variant allele frequencies and databases including gnomAD and dbSNP.

## RESULTS

### Clinical Information

Clinical and demographic information is summarized in Table 1. The 22 cases of sinonasal TCS were identified in 13 males and 9 females with a mean age of 45 years (range: 18 to 67 y). Tumors were generally large, with a mean size of 6.1 cm (range: 1.5 to 10.2 cm). There were 18 tumors (82%) centered in the nasal cavity, 2 (9%) in the maxillary sinus, 1 (5%) in the ethmoid sinus, and 1 (5%) in the mastoid bone, although 10 (45%) presented at high stage with involvement of multiple sinonasal subsites and the skull base. Of the 17 patients with treatment information available, 10 (59%) were treated with surgery, external beam radiation, and chemotherapy, 6 (35%) underwent surgery alone, and 1 (6%) completed surgery and radiation. Detailed follow-up information was available for 15 patients, with a median duration of 9 months (range: 1 to 118 mo). After treatment, 4 patients (27%) developed distant metastasis, and 3 patients (20%) experienced persistent local disease. At last available follow-up, 7 patients (47%) had no evidence of disease, 4 patients (27%) had died of disease, 3 patients (20%) were alive with disease, and 1 patient (7%) had died of postsurgical complications.

### Histologic Features

Histologic sections highlighted diverse cellular constituents in all sinonasal TCS, as illustrated in Figure 1. The majority of tumors demonstrated a predominance of primitive undifferentiated and neuroepithelial elements with rare areas of neuropil and rosette formation. All cases also contained prominent epithelial differentiation, including both squamous and glandular components. Although most of these squamous and glandular foci demonstrated a classic fetal-like clear cell appearance, there were rare areas with more mature keratinizing squamous epithelium and mucinous glands with intestinal features. The mesenchymal components were the most variable in both quantity and histologic appearance, but were relatively focal in most tumors. They showed a predominance of undifferentiated fibroblastic-like spindled cells with a broad spectrum of cytologic atypia and occasional areas of rhabdomyoblastic, osteoblastic, and chondroblastic differentiation.


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**TABLE 1.** Clinical and Demographic Information

| Case No. | Age (y) | Sex | Size (cm) | Location | Treatment | Course | Follow-up (mo) | Status |
|---|---|---|---|---|---|---|---|---|
| 1 | 57 | Male | 10.2 | Left nasal cavity, ethmoid, cribriform plate, and anterior cranial fossa | Surgery, chemotherapy, XRT | No progression | 36 | NED |
| 2 | 50 | Female | 6 | Left nasal cavity and ethmoid sinus | Surgery | Persistent local disease | 3 | AWD |
| 3 | 66 | Male | NA | Right nasal cavity | NA | NA | NA | NA |
| 4 | 54 | Male | NA | Left nasal cavity and maxillary sinus | NA | NA | NA | NA |
| 5 | 55 | Male | 7 | Left ethmoid sinus with involvement of all sinuses and nasal cavity | Surgery, chemotherapy, XRT | No progression | 118 | NED |
| 6 | 63 | Female | 8.2 | Right maxillary sinus, nasal cavity, and frontal, ethmoid, and sphenoid sinuses | Surgery, chemotherapy, XRT | Brain and lung metastasis | 13 | DOD |
| 7 | 37 | Male | 6.2 | Left nasal cavity, sphenoid, frontal, and ethmoid sinuses, and base of skull | Surgery, chemotherapy, XRT | Persistent local disease in skull base | 9 | DOD |
| 8 | 45 | Male | NA | Right nasal cavity | Surgery, XRT | Lung metastasis | 7 | DOD |
| 9 | 27 | Female | NA | Right nasal cavity | NA | NA | NA | NA |
| 10 | 18 | Male | 8.5 | Nasal cavity | Surgery, chemotherapy, XRT | No progression | 40 | NED |
| 11 | 30 | Male | 5.5 | Nasal cavity | Surgery, chemotherapy, XRT | No progression | 36 | NED |
| 12 | 67 | Male | 4 | Right nasal cavity and ethmoid sinus | Surgery, chemotherapy, XRT | Lung metastasis | 14 | AWD |
| 13 | 23 | Female | 4 | Right nasal cavity | Surgery, chemotherapy, XRT | Dural metastasis | 3 | AWD |
| 14 | 35 | Female | NA | Nasal cavity | NA | NA | NA | NA |
| 15 | 35 | Male | 7 | Nasal cavity | Surgery | NA | NA | NA |
| 16 | 36 | Female | 5.5 | Right nasal cavity | Surgery | NA | NA | NA |
| 17 | 39 | Male | 4 | Right mastoid | Surgery | Persistent local disease with brain invasion | 3 | DOD |
| 18 | 50 | Female | 9 | Bilateral nasal cavities and bifrontal sinuses | Surgery | Died of postsurgical complications | 1 | DOC |
| 19 | 27 | Female | 1.5 | Nasal cavity | NA | NA | NA | NA |
| 20 | 62 | Male | 4.5 | Left maxillary, sphenoid, and ethmoid sinuses | Surgery | No progression | 2 | NED |
| 21 | 67 | Female | 7 | Right nasal cavity and sphenoid sinus | Surgery, chemotherapy, XRT | No progression | 60 | NED |
| 22 | 54 | Male | 5.8 | Right nasal cavity | Surgery, chemotherapy, XRT | No progression | 9 | NED |

AWD indicates alive with disease; DOC, dead of other causes; DOD, dead of disease; NA, not available; NED, no evidence of disease; XRT, external beam radiation therapy.

## IHC Results

Results of IHC are tabulated in Table 2 and illustrated in Figures 2 and 3. Staining demonstrated loss of SMARCA4 expression in 18 cases of TCS (82%). In 15 cases (68%), the loss was diffuse across epithelial, mesenchymal, and neuroepithelial tumor elements despite retained strong and homogenous expression in background endothelial and other normal stromal cells. In 3 cases (14%), there was partial SMARCA4 loss, with reduced staining in epithelial and neuroepithelial elements and complete loss in stromal elements. In 4 cases (18%), SMARCA4 was completely intact. Although 8 cases (57%) demonstrated intact SMARCB1 expression, 6 (43%) showed reduced expression. There were 14 tumors (93%) that also showed partial loss of SMARCA2 expression, and all 15 (100%) showed variable positivity for Claudin-4. In most cases, the SMARCB1, SMARCA2, and Claudin-4 expression tended to be diffuse to patchy in epithelial elements but reduced to absent in neuroepithelial and stromal elements.

SMARCA4 expression was intact by IHC in almost all other sinonasal carcinomas and neuroendocrine tumors tested, including all squamous cell carcinomas (n = 83), sinonasal undifferentiated carcinomas (SNUCs) (n = 17), olfactory neuroblastomas (n = 12), small cell neuroendocrine carcinomas (n = 7), adenocarcinomas (n = 6), adenosquamous carcinomas (n = 6), mucoepidermoid carcinomas (n = 4), large cell neuroendocrine carcinomas (n = 3), NUT carcinomas (n = 3), human papillomavirus-related multiphenotypic sinonasal carcinomas (n = 1), sarcomatoid carcinomas (n = 1), and adamantinoma-like Ewing sarcomas (n = 1). Although 7 SMARCB1-deficient sinonasal carcinomas (88%) demonstrated intact SMARCA4, 1 case (13%) showed patchy loss of SMARCA4 expression.

## NGS Results

Targeted NGS results for the 3 cases of SMARCA4-deficient TCS that underwent sequencing are summarized

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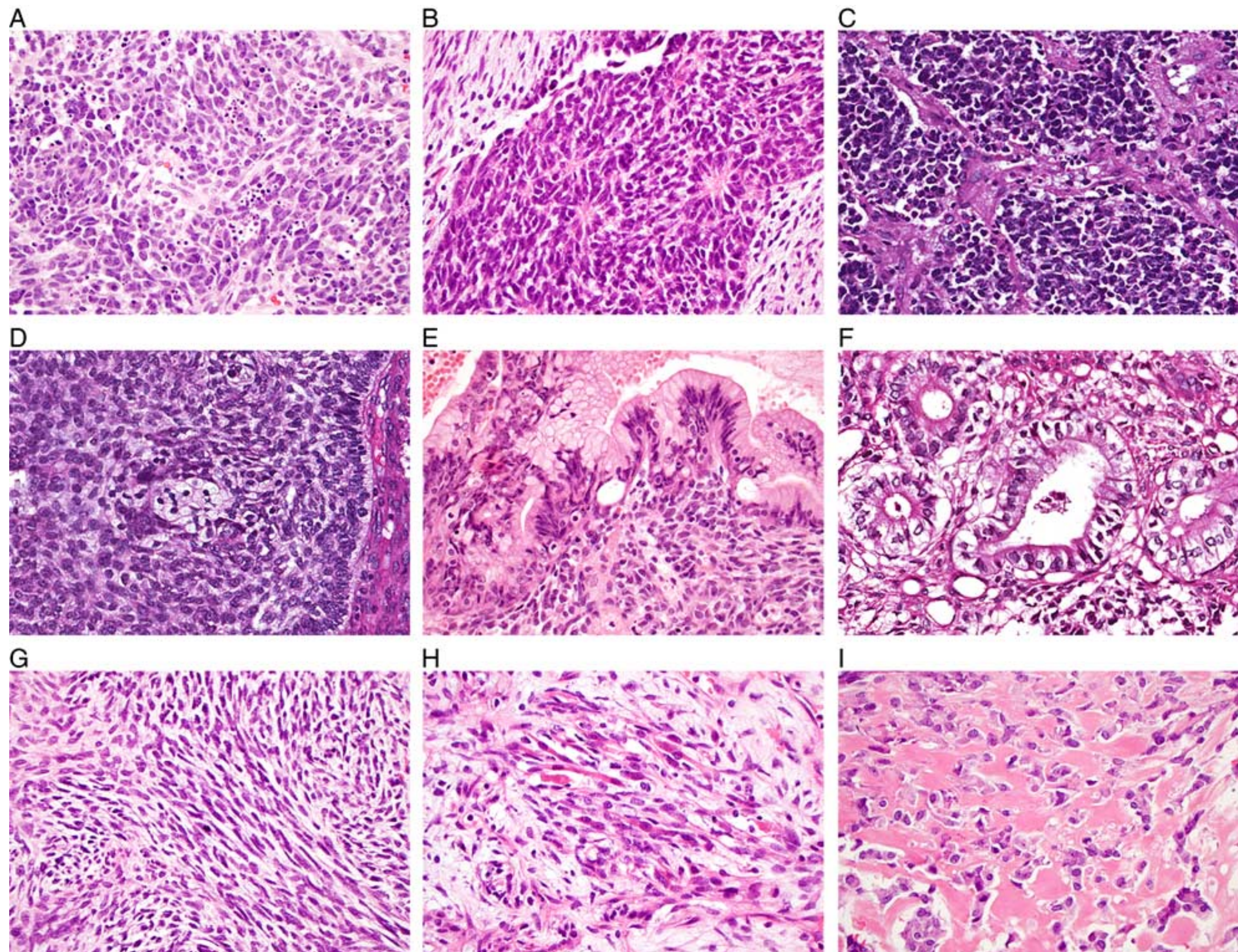


**FIGURE 1.** Most cases of TCS displayed a predominant component of primitive neuroepithelial cells with a high mitotic rate and prominent areas of necrosis and apoptosis (A), focal rosette formation (B), and rare areas of nested growth with prominent vascular stroma (C). There were also prominent epithelial elements including squamous (D) and glandular (E) components that frequently showed fetal-like clear cell change (F). The mesenchymal elements commonly consisted of nonspecific spindle-cell stromal proliferations (G), with occasional rhabdomyoblastic elements (H) or production of matrix such as osteoid (I).

in Table 3. NGS confirmed biallelic somatic inactivation of *SMARCA4* in all 3 cases. Mechanisms for inactivation included copy number loss affecting chr19p13.2 (n = 2), frameshift mutation (n = 2), intronic substitution affecting a splice site (n = 1), and nonsense mutation (n = 1). No other mutations of known oncogenic function were identified in this group of tumors, although all 3 also demonstrated variants of unknown significance in several other genes and 2 showed a wide range of copy number alterations with uncertain clinical relevance.

## DISCUSSION

Over the past decade, molecular analysis has reshaped the landscape of high grade sinonasal carcinomas, with recognition of novel tumor types and identification of recurrent genetic mutations in established entities that have blurred the lines between traditional and emerging categories. However, sinonasal TCS, a rare and aggressive sinonasal malignancy defined by the presence of teratomatous, carcinomatous, and sarcomatous elements, has remained poorly understood. Not only has the characteristic multiphenotypic differentiation seen in TCS engendered persistent controversy about its histogenesis, but its heterogenous morphologic appearance has also led to diagnostic overlap with a wide range of other tumor types. In this study we performed IHC and NGS on a cohort of sinonasal TCS to help clarify its classification and facilitate more specific diagnosis.

First, this study demonstrates recurrent loss of SMARCA4 in sinonasal TCS. *SMARCA4* is a gene located on chromosome 19p13.2 that encodes a key catalytic subunit of the switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complex.[22,23] Although *SMARCB1*, the gene that encodes a core subunit of this complex, is best known as a driver of various primitive and rhabdoid malignancies, mutations in other SWI/SNF complex members including *SMARCA4* are also commonly implicated in tumorigenesis.[24] Indeed, *SMARCA4* inactivation is the defining genetic event

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**TABLE 2.** IHC Results

| Case No. | SMARCA4 | SMARCB1 | SMARCA2 | Claudin-4 |
|---|---|---|---|---|
| 1 | Lost | Intact | Reduced | Variable |
| 2 | Reduced | Reduced | Reduced | Variable |
| 3 | Intact | NA | NA | NA |
| 4 | Intact | NA | NA | NA |
| 5 | Lost | Intact | Reduced | Variable |
| 6 | Lost | Reduced | Reduced | Variable |
| 7 | Lost | Intact | Reduced | Variable |
| 8 | Lost | NA | NA | NA |
| 9 | Reduced | NA | NA | NA |
| 10 | Lost | Intact | Reduced | Variable |
| 11 | Lost | Intact | Reduced | Variable |
| 12 | Lost | Reduced | Reduced | Variable |
| 13 | Lost | Reduced | Reduced | Variable |
| 14 | Intact | NA | NA | NA |
| 15 | Lost | Reduced | Reduced | Variable |
| 16 | Lost | Reduced | Reduced | Variable |
| 17 | Lost | Intact | Reduced | Variable |
| 18 | Lost | Intact | Reduced | Variable |
| 19 | Reduced | NA | NA | NA |
| 20 | Lost | NA | Reduced | NA |
| 21 | Lost | Intact | NA | Variable |
| 22 | Intact | Intact | Intact | Variable |

NA indicates not available.

in small cell carcinoma of the ovary, hypercalcemic type[25–27] and emerging groups of undifferentiated uterine and thoracic neoplasms and sinonasal carcinomas.[9,28–33] It also has been reported as the driver of rare atypical teratoid/rhabdoid tumors, epithelioid sarcomas, and malignant rhabdoid tumors that are *SMARCB1*-intact[34–37] and as a secondary mutation in subset of de-differentiated carcinomas in various organs.[38–41] In this study, complete loss of SMARCA4 expression was seen in 68% of TCS by IHC, with NGS confirmation of biallelic *SMARCA4* inactivation in the absence of other known oncogenic driver mutations in 3 representative cases. Of course, further molecular evaluation of cases with partial or intact SMARCA4 IHC expression will be necessary to fully characterize the genetic underpinnings of this tumor type and assess what role mutations in other genes such as *CTNNB1* may play.[18] However, these findings suggest that TCS is defined by recurrent somatic mutations in tumor-suppressor genes and point to *SMARCA4* loss as the most common such genetic event.

Recognition of recurrent *SMARCA4* inactivation in TCS also expands understanding of the role this gene plays in sinonasal tumorigenesis. Although > 75 cases of SMARCB1-deficient sinonasal carcinoma have been reported to date, including numerous examples uncovered among tumors previously classified as SNUC,[1–3,42,43] the frequency and significance of *SMARCA4* inactivation in the sinonasal tract was initially unclear because early studies only identified rare SMARCA4-deficient tumors.[5,44] More recently, however, several additional SMARCA4-deficient sinonasal carcinomas have been recognized, with 13 cases now documented in the literature.[9,11] These studies suggest the majority of SMARCA4-deficient sinonasal carcinomas have a neuroendocrine-like phenotype, with frequent but variable positivity for synaptophysin, and have initially been classified as small cell or large cell neuroendocrine carcinomas rather than SNUC.[9] As such, SMARCA4-deficient sinonasal carcinoma is emerging as a rare but seemingly distinctive subtype of sinonasal carcinoma. Identification of SMARCA4 loss in sinonasal TCS suggests that this genetic event is not limited to this small subgroup of primitive carcinomas but rather plays a more extensive role in the sinonasal tract than previously recognized. As targeted therapies with Enhancer of Zeste Homolog 2 (EZH2) and Cyclin-Dependent Kinase 4/6 (CDK4/6) inhibitors emerge as a potential tool for treating tumors with *SMARCA4* inactivation,[45–48] expanded recognition of similar mutations in TCS may open the door to new therapeutic opportunities for managing these aggressive sinonasal malignancies.

Indeed, molecular, IHC, and morphologic similarities between sinonasal TCS and SMARCA4-deficient sinonasal carcinoma raise the possibility that these tumors are part of the same spectrum rather than separate entities. The undifferentiated small cell morphology and positivity for neuroendocrine markers seen in SMARCA4-deficient sinonasal carcinoma is reminiscent of the dominant neuroepithelial component in TCS. Furthermore, 2 cases of SMARCA4-deficient sinonasal carcinomas have been reported with divergent differentiation, including combined small cell/squamous and neuroendocrine/glandular features, paralleling the multilineage elements seen in TCS.[11] Conversely, variable positivity for tight-junction protein Claudin-4, which has previously been reported to differentiate other epithelial and mesenchymal tumors with SWI/SNF loss,[49] points toward a true epithelial origin for TCS. This overlap suggests that sinonasal tumors with *SMARCA4* inactivation actually may show a continuum of differentiation ranging from a pure primitive carcinoma to the mixed elements of TCS. Such phenotypic heterogeneity is not entirely surprising as SMARCA4 loss can occur in tumors with both epithelial and mesenchymal differentiation, a small subset of which show intermixed elements of both lineages.[50,51] These multilineage tendencies likely stem from the key role chromatin remodeling plays in activating and inhibiting various pathways of differentiation.[52] Recognition of this diagnostic spectrum based on common *SMARCA4* mutations further blurs the lines between established and emerging sinonasal entities.

Beyond the continuum with SMARCA4-deficient sinonasal carcinomas, these findings also suggest that IHC loss of SMARCA4 may help confirm a diagnosis of TCS in a majority of cases. The diverse histologic components of TCS can mimic a broad range of other sinonasal tumors, including small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, squamous cell carcinoma, adenocarcinoma, olfactory neuroblastoma, and various sarcomas,[13–16,19,53] making it difficult to correctly classify TCS in limited material. The presence of at least partial loss of SMARCA4 expression in 82% of TCS, with complete loss in 68%, provides a promising additional tool for narrowing these differential diagnoses. Loss of SMARCA4 appears relatively specific for TCS and SMARCA4-deficient carcinoma in the sinonasal tract, with intact protein expression in virtually all other epithelial and neuroendocrine tumor types tested and partial loss in only 1 case of SMARCB1-deficient sinonasal carcinoma. Some overlap in expression of SWI/SNF family proteins is well-es-

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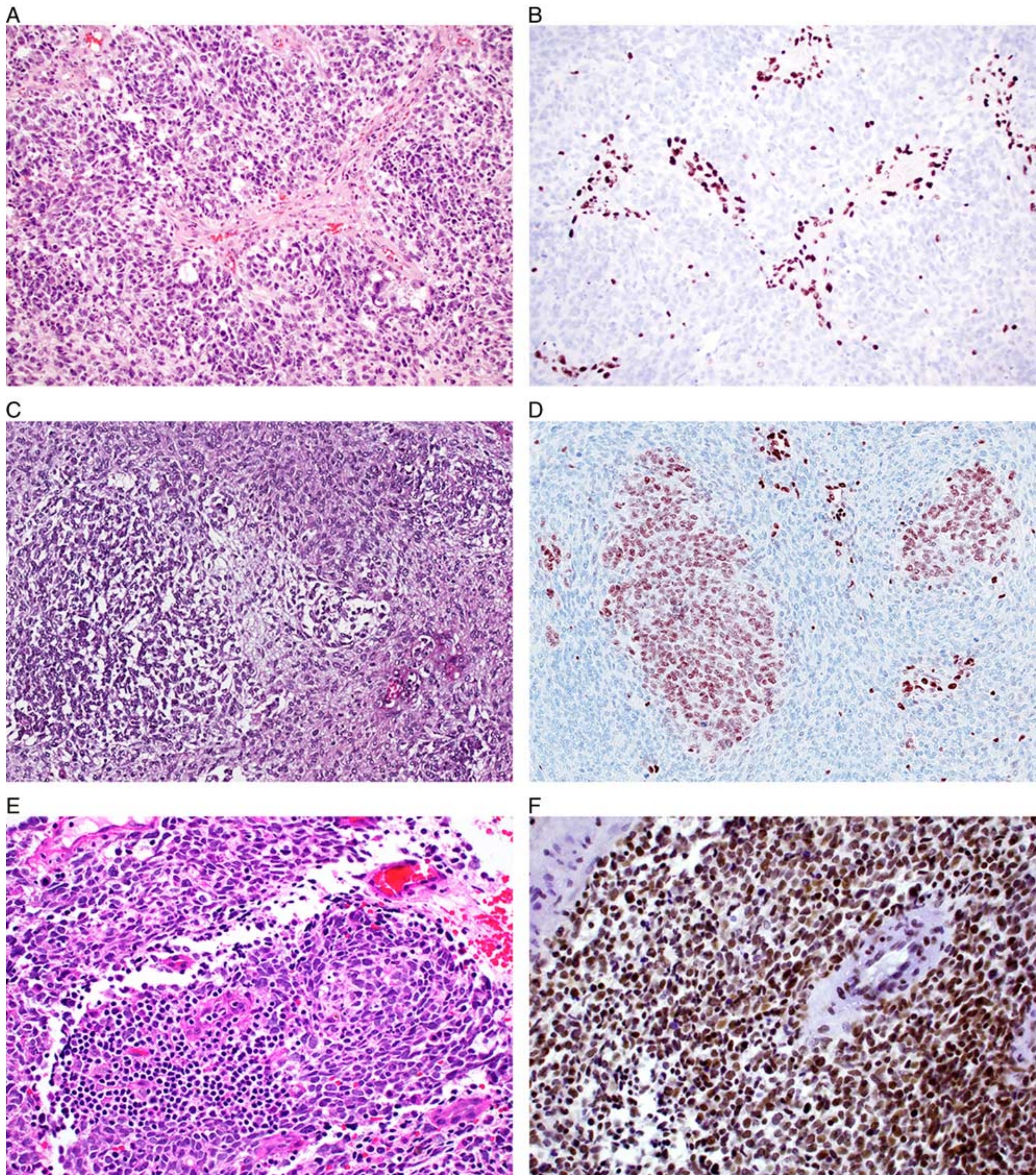


**FIGURE 2.** The majority of TCS demonstrated complete loss of SMARCA4 by IHC despite retained endothelial expression (A, B). However, a small group of tumors showed partial SMARCA4 loss (C, D) and another subset demonstrated intact SMARCA4 expression (E, F).

tablished in other organs, with frequent partial to complete loss of SMARCA2 expression with either *SMARCA4* or *SMARCB1* inactivation. However, partial SMARCB1 loss with *SMARCA4* inactivation or partial SMARCA4 loss with *SMARCB1* inactivation occurs much more rarely.[1,40,54] In those uncommon cases where there is overlap, performing SMARCA4 and SMARCB1 in tandem should help clarify the dominant player. Although further evaluation of expression in nonepithelial sinonasal tumors is necessary, SMARCA4 IHC promises to be a valuable diagnostic marker for TCS.


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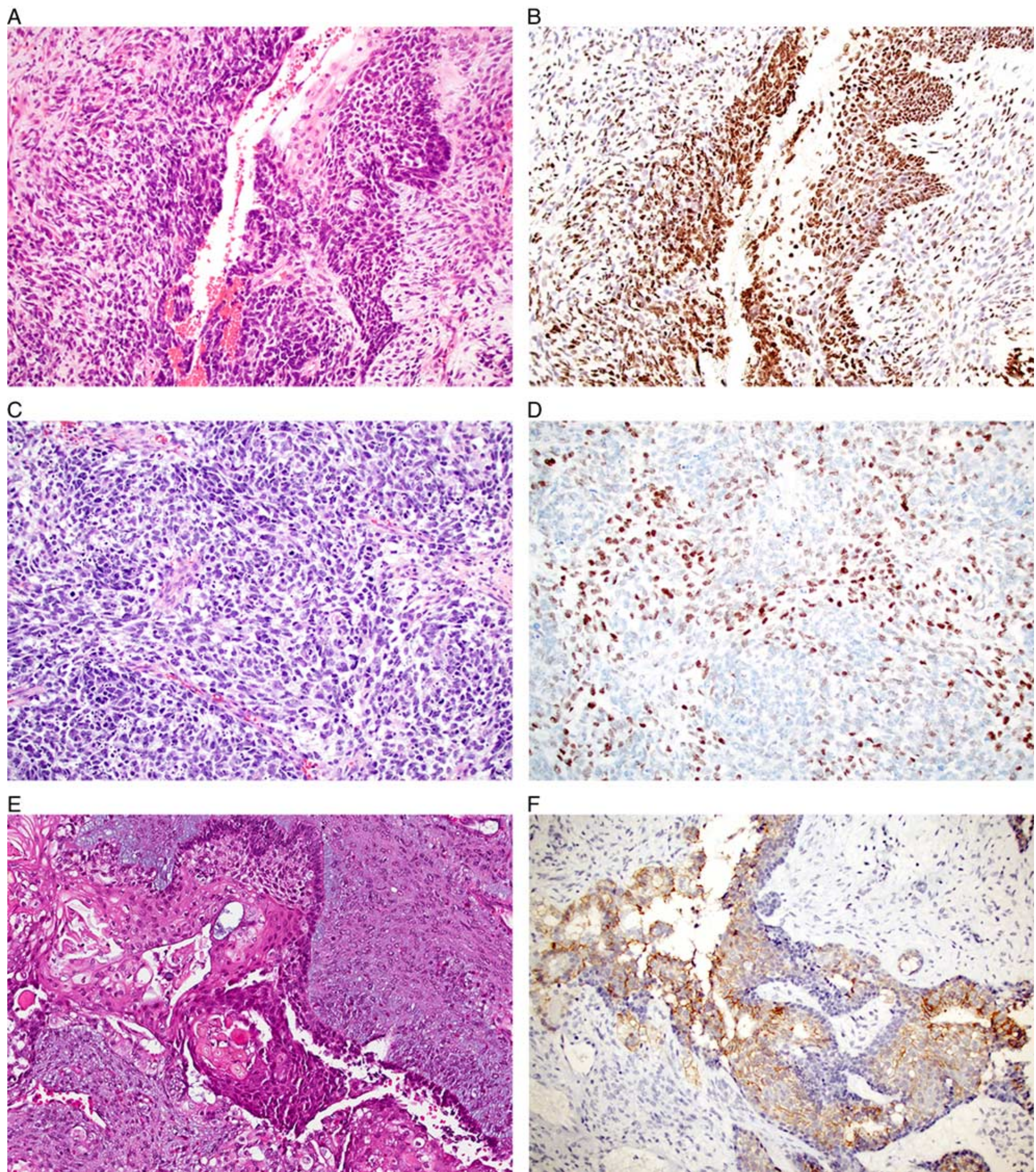


**FIGURE 3.** Although most cases of TCS showed intact SMARCB1 IHC, a subset demonstrated reduced expression (A, B). All cases of TCS also showed patchy loss of SMARCA2 (C, D) and variable expression of Claudin-4 (E, F) with increased expression in epithelial and neuroepithelial elements and loss in mesenchymal components.

In summary, we have identified recurrent IHC loss of SMARCA4 expression in a majority of sinonasal TCS cases with corresponding genetic inactivation of *SMARCA4*. These findings suggest that TCS is driven by recurrent mutations in tumor-suppressor genes, and that *SMARCA4* loss is the most common such mutation in this rare tumor type. Not only does this result expand understanding of the emerging role of *SMARCA4* in the sinonasal tract, but it also suggests that TCS is on a spectrum with SMARCA4-deficient sinonasal carcinomas

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**TABLE 3.** NGS Results

| Case No. | SMARCA4 Mutations (Variant Allele Frequency) | Other Mutations (Variant Allele Frequency) |
|---|---|---|
| 1 | SMARCA4 c.2616+2T > C (56%)<br>chr19p13.2 loss | KDM5A p.I324V (46%)<br>KMT2C p.G3334R (61%)<br>NBN p.T268M (39%)<br>NFE2L2 p.R43G (10%) |
| 5 | SMARCA4 p.D558fs (15%)<br>chr19p13.2 loss | BCL3 p.G276D (28%)<br>ESR1 p.S178Y (19%)<br>KMT2A p.G1990* (17%)<br>PPP3CA p.S353Y (15%)<br>SPTBN1 p.I756S (30%)<br>TP53BP1 p.L1751M (18%) |
| 6 | SMARCA4 p.M781fs (33%)<br>SMARCA4 p.Y834* (33%) | CDKN2B p.M8R (44%)<br>SPTBN1 p.K1815R (38%) |

*Standard genetic representing a stop codon.
Mutations and significant copy number alterations are included.

which show overlapping morphology and molecular characteristics, further realigning the taxonomy of high grade sinonasal tumors. IHC for SMARCA4 may also prove to be a valuable adjunct for the diagnosis of TCS in small biopsy material.

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