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Sinonasal Adenosquamous Carcinoma - Morphology and Genetic Drivers Including Low- and High-Risk Human Papillomavirus mRNA, *DEK*::*AFF2* Fusion, and *MAML2* Rearrangement

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Abstract

Background Sinonasal adenosquamous carcinoma is rare, and there are almost no studies detailing morphology or characterizing their genetic driver events. Further, many authors have termed sinonasal tumors with combined squamous carcinoma and glands as mucoepidermoid carcinoma but none have analyzed for the presence of *MAML2* rearrangement.

Methods Cases from 2014 to 2020 were collected and diagnosed using World Health Organization criteria. They were tested for p16 expression by immunohistochemistry (70% cut-off), *DEK*::*AFF2* fusion by fluorescence in situ hybridization (FISH) and AFF2 immunohistochemistry, *MAML2* rearrangement by FISH, and low- and high-risk HPV by RNA ISH and reverse transcription PCR, respectively. Detailed morphology and clinical features were reviewed.

Results There were 7 male (64%) and 4 female (36%) patients with a median age of 69 years, most Caucasian (10 of 11 or 91%). Most had tobacco exposure (8/11, 73%) and most presented with epistaxis, a visible nasal mass, and/or facial pain. Several had a precursor papillomas (3 of 11, 27%). The squamous component had variable keratinization, 5 of 11 (46%) of which would be described as keratinizing, 3 non-keratinizing, and 2 with mixed features. All had gland formation, by definition, and 2 of 11 (18%) had ciliated tumor cells. None of the 11 cases had *MAML2* rearrangement and one had *DEK*::*AFF2* fusion with associated positive nuclear AFF2 protein immunostaining. Most were p16 positive (7 of 11, 64%) and all 7 of these were hrHPV positive either by RNA ISH or RT-PCR. Two of the p16-negative tumors were positive for lrHPV by RNA ISH. Treatment included surgery alone (4 of 11, 36%), surgery with adjuvant radiation (5 of 11, 45%), and surgery with radiation and chemotherapy (2 of 11, 18%). Four of 11 patients (36%) suffered disease recurrence, two requiring re-operation and who were disease free at last follow-up, one receiving additional chemotherapy and who was alive with disease. The other elected to undergo palliative therapy and died of disease.

Conclusion Sinonasal adenosquamous carcinoma is a somewhat heterogeneous tumor not infrequently arising ex papilloma and having various drivers including high- and low-risk HPV and rarely *DEK*::*AFF2* fusion. The prognosis appears favorable when proper treatment is possible.

Keywords Nasal Cavity · Adenosquamous Carcinoma · Paranasal Sinus · *DEK*::*AFF2* · Low-risk HPV · High-risk HPV · *MAML2*

Introduction

Adenosquamous carcinoma (AdSCC) of the sinonasal tract is a rare entity with less than 100 reported cases in the English literature [1–5]. Sinonasal tumors with combined squamous carcinoma and gland formation have been regarded by some authors to represent mucoepidermoid carcinomas (MEC) arising from sinonasal minor salivary gland tissues, and some have even considered tumors like this arising in a background of sinonasal papilloma ("ex papilloma") as MEC. [6, 7]. However, based on surface mucosal involvement, overt squamous differentiation (rather than just being squamoid or epidermoid), and the immunohistochemical phenotype of the tumors, it is more generally thought that AdSCC is a subtype of SCC [8]. The World Health

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Organization (WHO) specifically defines AdSCC [9] as a tumor with a biphasic morphology containing both squamous and adenocarcinomatous components that are distinct but in close proximity to each other [10]. While there is some morphologic overlap with MEC, AdSCC is typically associated with dysplasia of the surface epithelium and consistently demonstrates keratinizing squamous differentiation [11], which is rare in MEC. Additionally, most MECs have been shown to harbor a tumor-type specific translocation fusion gene *CRTC1::MAML2*[12, 13]. Clinically, AdSCC behaves more aggressively than both MEC and conventional (keratinizing) SCC[1, 2, 4, 14, 15]. AdSCC, across all head and neck anatomic subsites, has a 3-year survival rate of 52% and a median survival time of 39 months with up to 80% of patients developing nodal and/or distant metastases [1, 5]. In contrast, metastasis and death from MEC are relatively uncommon [16]. Due to the rarity of sinonasal AdSCC, there are almost no studies detailing morphology or characterizing genetic driver events, such as transcriptionally active human papillomavirus (HPV) [17, 18] or *DEK::AFF2* fusion [19–22]. Further, despite the relatively frequent confusion between sinonasal AdSCC and MEC, no studies have examined for the presence of *MAML2* rearrangement in these patients. In this study, we examined 11 cases of sinonasal adenosquamous carcinoma, characterized their morphology, and evaluated for key driver events.

Materials and Methods

A natural language search of surgical pathology reports for specimens examined at the Vanderbilt University Medical Center from 2014 to 2020 was performed to identify cases diagnosed as sinonasal AdSCC. Cases were examined microscopically and confirmed as AdSCC using WHO diagnostic criteria [9, 10]. After gathering the patients from Vanderbilt University Medical Center, three cases from collaborators at the University of Miami and the Ohio State University were acquired (from 2021 to 2022). The diagnosis required the presence of distinct areas of invasive SCC intermixed with nests with punched-out (smooth) luminal spaces, with or without intraluminal mucin. Some tumors had goblet cells with intracytoplasmic mucin. As supported by prior studies and the WHO criteria [9], there was no lower percentage cut-off for the amount of glandular or squamous differentiation. If a papilloma component was present, it was diagnosed using WHO criteria, as well. Detailed morphologic characterization of each case was performed, and clinical and demographic data were collected for all patients. The fraction of surface area occupied by glands and/or goblet cells relative to SCC was semiquantitated in 5% increments. Mitotic activity was semiquantitated as very low (almost none detectable), low (occasional mitotic figures), medium

(mitotic figures easily found), high (mitotic figures in almost every field), and very high (multiple mitotic figures in every field).

p16 Immunohistochemistry

Immunohistochemistry was performed for p16 on formalin-fixed, paraffin-embedded tissue sections. For the in-house cases, testing utilized the E6H4 antibody (prediluted; Ventana Medical Systems, Inc.) on a Leica Bond automated instrument (Leica Biosystems, Inc.) with antigen retrieval consisting of 10 min in the ER1 proprietary antigen retrieval solution. Primary antibody solution was diluted using Leica's BOND primary antibody diluent. The Bond Polymer Refine detection system was used for visualization. Slides were then dehydrated, cleared, and coverslipped. Staining was interpreted by one-study pathologist (JSL), using the CAP recommendation [23] defined in oropharyngeal SCC for p16 as a surrogate of high-risk HPV (positive = nuclear and cytoplasmic positivity in > 70% of tumor cells of at least moderate to strong intensity). For the 3 outside cases, p16 immunohistochemistry was performed and interpreted in routine clinical practice at the respective institution using the same interpretation criteria.

HPV Testing

For high-risk HPV, RT-PCR was performed using RNA extracted from two 10-µm unstained slides which were selected for tumor containing areas from the corresponding H&E slides [24]. Testing was performed for E6 and E7 mRNA transcripts of the most common 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 52, 56, 58, 59, 66, and 68) [24]. RNA Extraction was performed with Qiagen miRNeasy FFPE kit (QIAGEN Sciences Inc., Gaithersburg, MD) and resulted in between 0.5 and 5 µg of RNA, depending on tumor size. All oligo primers in the assays were purchased from Sigma-Aldrich (St Louis, MO, USA). The reverse transcription reaction was done with the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems). The RT-PCR mixture contained 150 ng of RNA and was incubated at 25 °C for 20 min, 37 °C for 60 min and then 85 °C for 5 min. qPCR was then performed to quantify the cDNA product using Power SYBR Green PCR Master Mix (Applied Biosystems) and 500-nM HPV-type specific primers. Each HPV assay for E6 or E7 from 13 HPV types was individually performed in a separate well on a 384-well PCR plate. The PCR protocol was 95 °C for 10 min and then 36 cycles of amplification (95 °C for 10 s, 58 °C for 15 s, and 60 °C for 15 s). GAPDH and β-actin were included as expression reference controls for qPCR data normalization

(normalized to the average expression of these two control genes). Quantitation was expressed as normalized threshold PCR cycle number [24].

For the in-house cases, low-risk HPV in situ hybridization for E6/E7 mRNA was performed by Propath Laboratories (Dallas, TX) using the RNAscope® 2.5 HD—BROWN Manual Assay (Advanced Cell Diagnostics, Inc., Hayward, CA) targeting HPV-associated RNA in the nucleus and cytoplasm of the target cells. Tissue samples that previously stained positive for low-risk HPV, as well as some that were negative, were used as batch control tissues and reacted appropriately. Probes cover HPV types 6, 11, 42, 43, and 44. Cases were read by a single-study pathologist (JSL) and classified in a binary manner as either positive or negative. For one of the outside cases, lrHPV RNA in situ hybridization had been performed as part of clinical practice, and for three of the outside cases, hrHPV RNA in situ hybridization had been performed as part of clinical practice.

DEK Fluorescence In Situ Hybridization (FISH) and AFF2 Immunohistochemistry

DEK FISH was performed using a break-apart probe (catalog no.: CT-PAC347; CytoTest, Rockville, MD, USA) as previously described [20]. The result was considered positive with more than 20% of nuclei showing break-apart signals in 50 non-overlapping tumor cells. AFF2 immunohistochemistry was performed using an anti-AFF2 antibody (HPA003139, dilution 1:100, Sigma-Aldrich, St. Louis, MO, USA) as previously described [22]. The result was considered positive with nuclear expression of any intensity in more than 30% of the tumor cells.

Results

In total, 8 cases from the Vanderbilt University Medical Center were confirmed as AdSCC from our original database search. An additional 3 more recently diagnosed cases from collaborators were also identified for a total of 11 cases. All 11 cases examined were from surgical resection specimens. The clinical and pathologic features for all patients are shown in Table 1. There were 7 (64%) males and 4 (36%) females ranging in age from 50 to 74 (mean, 63.8, median 69.0). Primary cross-sectional imaging was available for 10 of 11 patients with 9 (82%) having an identifiable mass. The most common primary location for tumors was the nasal septum, 5 of 11 cases (45%), but tumors also arose in the maxillary sinus (2 of 11, 18%), ethmoid sinus (1 of 11, 9%), and nasal dorsum (1 of 11, 9%). In one patient, a nasal cavity tumor extended to involve the right medial canthus (1 of 9, 11%).

Table 1 Clinical Features

Clinical Features	
Demographics	
Male	7 (64%)
Female	4 (36%)
Age (years and SD)	64 ± 9
Ethnicity	
Caucasian	10 (91%)
African American	1 (9%)
Alcohol Exposure	4/11 (36%)
Smoke Exposure	8/11 (73%)
Locations	
Nasal Septum	5/11 (45%)
Maxillary Sinus	2/11 (18%)
Ethmoid Sinus	1/11 (9%)
Inner Canthus (Eye)	1/11 (9%)
Nasal Vestibule	1/11 (9%)
Nasal Dorsum	1/11 (9%)

SD Standard deviation

Tobacco use was common, with 8 of 11 patients (73%) endorsing frequent exposure. Alcohol use was less, with only 4 of 11 patients (36%) reporting consumption. Patients were treated either with surgery alone (4 of 11, 36%), surgery plus postoperative radiation (5 of 11, 45%), or surgery plus postoperative radiation and chemotherapy (2 of 11, 18%). The patients were followed for an average of 13.97 months (range 0.5–28) with 4 of 11 patients (36%) experiencing a recurrence and only 1 of those 4 patients dying of disease (10 months postoperatively).

The histopathologic features for all patients are shown in Table 2. The most common features were those essentially necessary for the diagnosis of AdSCC, namely goblet cells (11/11, 100%), mucin (11/11, 100%), tubuloglandular formation (10/11, 91%), and involvement of surface epithelium (10/11, 91%) (Figs. 1 and 2). Other less common features were fibrosis/desmoplasia (10/11, 91%) and keratin pearl formation (4/11, 36%). The adenocarcinoma/gland-forming component varied significantly in extent across the different tumors (range 5–70%) but was, by surface area, the minor one in most cases (average 35%). The squamous component was conventional (keratinizing) in 5 of 11 cases (45%), non-keratinizing in 3 of 11 cases (27%), and mixed areas of both keratinizing (Fig. 1) and non-keratinizing in 2 of 11 cases (18%) (Fig. 3). Intercellular bridges could only be identified within the squamous component in 5 of 11 cases (45%) and only 1 of 11 (9%) cases showed a pattern of cellular discohesion. Interestingly, within the adenocarcinomatous portion of our tumors, cilia were identified in 2 out of 11 cases (18%) (Fig. 4). A

Table 2 Histopathologic Features

Case	1	2	3	4	5	6	7	8	9	10	11
Mucosal surface involvement	Y	Y	Y	Y	N	Y	Y (focal)	Y	Y	Y	Y
Keratin pearls	Y (focal)	Y (focal)	N	N	Y (focal)	Y (multifocal)	N	N	N	N	N
Intercellular bridges	N	N	N	N	N	Y (focal)	Y (focal)	Y (focal)	Y (focal)	Y (focal)	N
Cellular discohesion	Y (focal)	N	N	N	N	N	N	N	N	N	N
Maturing squamous differentiation	Y (focal)	Y (multifocal)	N	N	Y (focal)	Y (multifocal)	N	Y (focal)	Y (focal)	Y (focal)	N
Non-keratinizing features	Y	N	Y (focal)	Yes (extensive)	Y	N	N	N	N	N	Y
Perineural invasion	N	N	N	N	Y (multifocal)	N	N	N	N	N	Y (multifocal)
Vascular invasion	N	N	N	N	N	N	N	N	N	N	N
Tubuloglandular formation	Y (focal)	Y (extensive)	N	Y (multifocal)	Y (multifocal)	Y (multifocal)	Y (multifocal)	Y (multifocal)	Y (extensive)	Y (extensive)	Y (multifocal)
Mucin	Y (focal)	Y (multifocal)	Y (extensive)	Y (multifocal)	Y (focal)	Y (multifocal)	Y (multifocal)	Y (multifocal)	Y (multifocal)	Y (multifocal)	Y (multifocal)
Goblet cells	Y (focal)	Y (focal)	Y (extensive)	Y (focal)	Y (focal)	Y (multifocal)	Y (multifocal)	Y (multifocal)	Y (multifocal)	Y (multifocal)	Y (multifocal)
Cilia	Y (focal)	N	N	N	N	N	N	Y (focal)	N	N	N
Fraction Surface Area Consisting of Glands and/or Goblet Cells (%)	5	40	20	30	40	15	50	30	60	70	30
Pre-existing papilloma	N	N	Y (inverted)	N	Y (inverted)	N	N	Y (exophytic)	N	N	N
Nuclear pleomorphism	Mild	Moderate, focally marked	Mild	Marked diffuse	Mild to moderate	marked (focal)	moderate focal	moderate	Mild	Mild	Marked diffuse
Dystrophic calcification	N	N	N	N	N	N	Y (focal)	N	N	N	N
Necrosis (% surface area)	N	N	N	multifocal (15%)	N	N	N	N	N	N	N
Fibrosis/desmoplasia	N	Y (focal)	Y (extensive)	Y (focal)	Y (multifocal)	Y (multifocal)	Y (focal)	Y (multifocal)	Y (multifocal)	Y (extensive)	Y (multifocal)

Table 2 (continued)

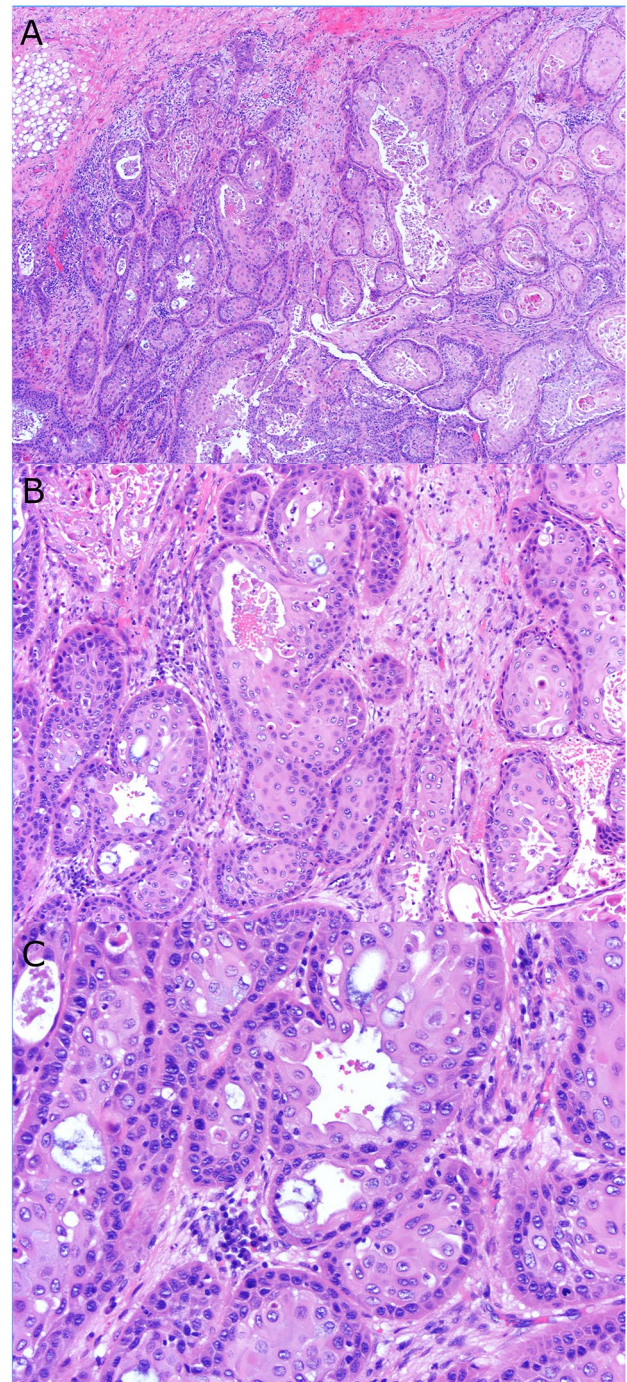| Case	1	2	3	4	5	6	7	8	9	10	11
Nuclear shape	Round	Round	Round/grooved	Round/oval	Round/oval	Round	Round	Round/oval/angulated	Round	Round/oval	Round/oval
Mitotic activity	Very Low	Medium	Low	High	High	High	High	Very Low	Medium	High	Very High

Y Yes, *N* No, *N/A* Not Available

Fig. 1 Typical sinonasal AdSCC (Case 6) with keratinizing-type SCC component consisting of **A** variably sized nests of solid and cystic tumor invading the submucosa. **B** Solid nests of keratinizing SCC with smaller peripheral basal cells and central keratinized cells with abundant, eosinophilic cytoplasm, mixed with foci of gland formation with smooth luminal borders and mucocytes. **C** High power showing the moderate nuclear pleomorphism of the tumor cells and scattered mucocytes, mitotic figures, and apoptotic bodies
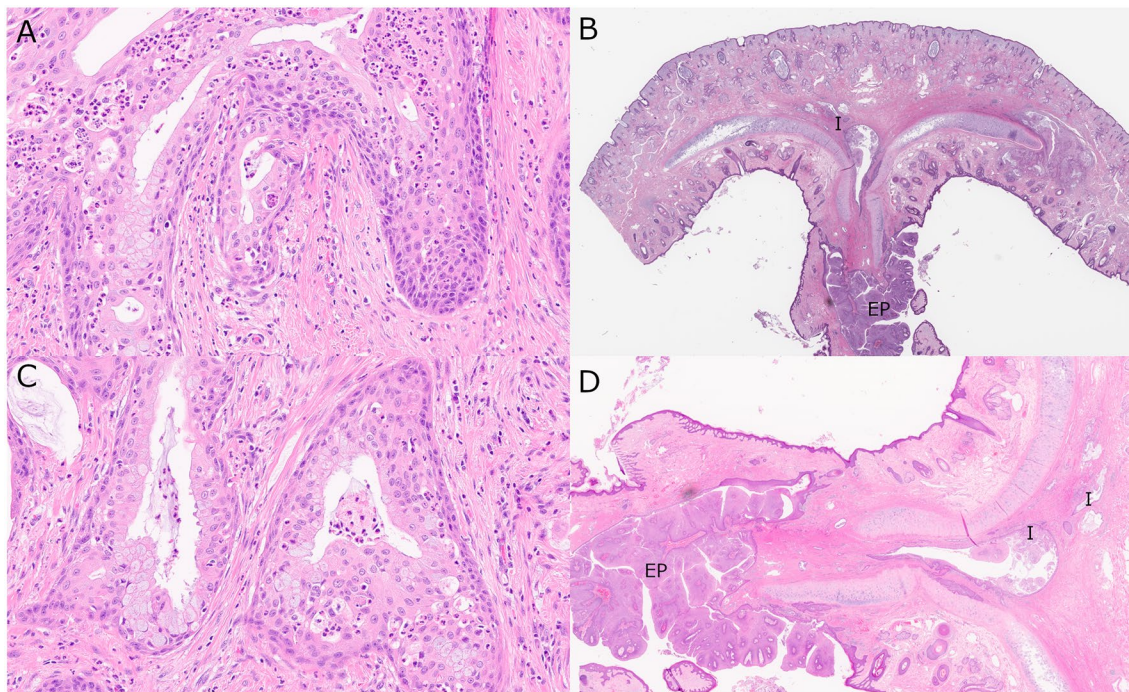
Fig. 2 Exophytic papilloma-associated AdSCC (Case 8) showing **A** an invasive biphasic tumor composed of cuboidal surface cells, some with intracytoplasmic mucin, and with underlying immature squamous epithelium with cells with eosinophilic cytoplasm. **B** Invasive tumor emerging from the base of a nasal septal exophytic papil-loma (I=invasive; EP=papilloma). **C** On higher power, the mucus cells are more obvious and an infiltrate of neutrophils is present within the epithelium. **D** High power shows the exophytic papilloma with a few nests of invasive AdSCC with dilated, mucin-filled lumina invading anteriorly into the septum and nasal vestibule

precursor lesion was identified in 3 of 11 cases (27%) with 2 of 3 (66%) showing inverted sinonasal papillomas and 1 of 3 (33%) showing exophytic papilloma (Fig. 2).

Tumor cells showed marked nuclear pleomorphism in 4 of 11 cases (36%) (Fig. 3), ranging from focal to diffuse, with 3 of 11 (27%) showing moderate nuclear pleomor-phism, and 4 cases (36%) showing only mild pleomorphism. The nuclear shape was typically round (5/11, 45%) or round to ovoid (4/11, 36%). Dystrophic calcification and necrosis were only seen in 1 case (9%) each. Mitotic activity var-ied between tumors with 1 of 11 cases (9%) demonstrating very high, 5 of 11 cases (45%) demonstrating high, 1 of 11 (9%) demonstrating medium, 1 of 11 (9%) demonstrat-ing low, and 2 of 11 (18%) demonstrating very low mitotic activity (Table 3).

The molecular and genetic testing for all patients is shown in Table 4. FISH testing for *MAML2* gene rearrangement showed all 9 cases tested to be negative (0%). p16 immuno-histochemical staining was positive in 7 of 11 cases (64%) using the 70% nuclear and cytoplasmic cut-off (Fig. 5). RNA in situ hybridization for high-risk HPV was positive in the 2 patients tested and reverse transcription PCR for high-risk HPV was positive in 7 of the 9 cases tested, so that, overall, 7 of 11 cases (all of which were also p16 positive) were tran-scriptionally active high-risk HPV-associated. An additional

2 patients were positive for transcriptionally active low-risk HPV by RNA in situ hybridization. Finally, 1 case (11%) was positive for *DEK::AFF2* gene fusion by FISH, which was confirmed by AFF2 immunohistochemistry showing extensive nuclear staining (Fig. 5).

Discussion

The current study is one of very few to detail the morphol-ogy and to characterize genetic driver events in sinonasal AdSCC. While there is some overlap in morphology between this entity and MEC, there are key differences morphologi-cally and, as shown in this study, in the genetic driver events.

Sinonasal AdSCC occurs primarily in the 6th decade of life on average with no particular sex predilection. The nasal septum is the most commonly affected site which may be secondary to the location containing respiratory epithe-lium more readily exposed to low- and high-risk HPV from pharyngeal reflux. The tumors are somewhat heterogene-ous in that they vary substantially in the amount of gland formation, the degree of mucus cell differentiation, and in the amount of mitotic activity and degree of nuclear atypia. Some are relatively bland, with minimal nuclear pleomor-phism, little mitotic activity (cases 1, 3, 9, 10), pushing
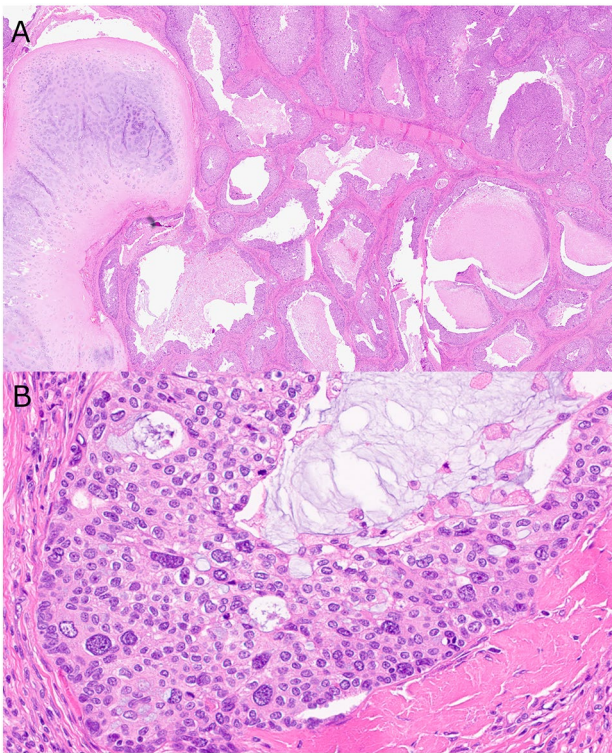
Fig. 3 AdSCC (Case 4) showing **A** variably sized partial solid and partially cystic glands with intraluminal mucin invading the stroma and around septal cartilage and **B** non-keratinizing SCC with marked nuclear pleomorphism

Fig. 4 *DEK::AFF2* fusion-associated AdSCC (Case 1) showing **A** a mixture of columnar glandular cells on the surface and around glands with mucus cells and underlying non-keratinizing SCC. **B** Surface columnar cells with terminal bars and cilia. Note the relatively bland cytologic appearance of the tumor

borders, and even rarely with tumor forming cilia. Others are markedly infiltrative with marked nuclear pleomorphism and mitotic activity (cases 2, 4, 6, 11). Some arise ex-sinonasal papilloma. The heterogeneity is reflected in their molecular features, with most tumors driven by transcriptionally active high-risk HPV, a few by low-risk HPV, and even occasional cases by *DEK::AFF2* fusion [19, 20, 22]. In all, we found a genetic "driver" in 10 of the 11 cases (90.9%).

The distinction between sinonasal tract AdSCC and MEC is somewhat difficult and has been a source of confusion in head and neck pathology [9] [2]. Many cases have been reported as sinonasal tract MEC, and some even reported as arising ex papilloma [6]. Sinonasal tract MECs have been reported as case reports and one larger series, by Wolfish et al. [7], of 19 cases from the Armed Forces Registry of Pathology (AFIP) and author consultation files. They reported that these represented 0.075% of all sinonasal tumors over the time period analyzed, giving an idea of their rarity [7]. The key distinguishing morphologic features between AdSCC and MEC are surface squamous dysplasia/involvement and maturing squamous differentiation, both of which, when present, favor AdSCC. While Wolfish et al. reported that they excluded tumors with keratinizing squamous differentiation, 6 of their cases did have surface
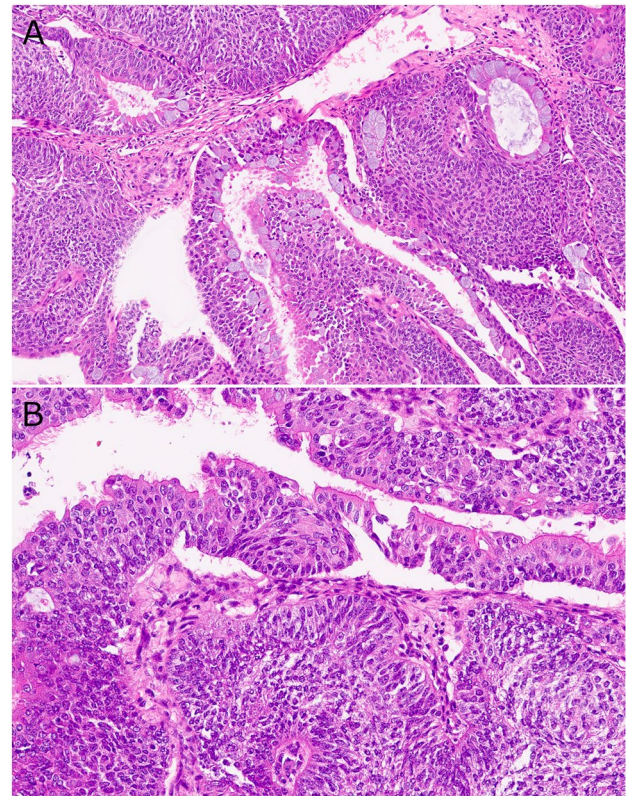
involvement which was reportedly difficult to tell as "arising from the surface" versus "involving the surface." They did not have any molecular testing. In our study, we found all 9 tested cases of AdSCC to be negative for *MAML2* rearrangement. This is supported by the data of Kass et al. [2], who analyzed AdSCC across the head and neck region for *MAML2* by FISH and found all 7 of their sinonasal tract cases to be negative for rearrangement. It seems that, given the rarity of what has been described as sinonasal tract MEC, one could be much more conclusive for that diagnosis by having positive rearrangement by *MAML2* FISH testing.

The prognosis of AdSCC has been found, in general, to be worse than that for conventional SCC across head and neck anatomic subsites [5, 15]. This was supported more specifically in the sinonasal tract by Vazquez et al. [4], who analyzed disease outcomes for sinonasal SCC and subtypes from the Surveillance, Epidemiology, and End Results (SEER) database. They found that of all the subtypes, AdSCC had the worst prognosis. There was no central review for tumor classification and no accounting for HPV status; however, so it is unclear how many of these 31 tumors really were strictly defined AdSCC, nor how many of these rare tumors were

Table 3 Additional pathologic features

Case	1	2	3	4	5	6	7	8	9	10	11
T stage	N/A	pT2	pT4a	pT3	N/A	pT4b	N/A	pT4a	pT4a	pT3	pT1
N stage	N/A	pNX	pN1	pN0	N/A	pN0	N/A	pNx	pNx	pN0	pN0
Mucicarmine	N/A	N/A	N/A	N/A	Positive	N/A	N/A	N/A	N/A	N/A	Positive
p40	N/A	N/A	N/A	Positive	N/A	N/A	N/A	N/A	Positive	Positive	Positive
p63	Positive	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Positive	N/A	Positive
Cytokeratin AE1/AE3	Positive	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ki67	15–20%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Precursor lesion	No	No	Inverted papilloma	No	Inverted papilloma	No	No	Exophytic papilloma	No	No	No

Table 4 Genetic Drivers

Case	*MAML2* FISH	*DEK::AFF2* FISH/IHC	p16 IHC	lrHPV mRNA	hrHPV mRNA RT-PCR	hrHPV mRNA ISH
1	−	+	−	+	−	NP
2	−	−	+	−	+	NP
3	−	−	−	−	−	NP
4	−	−	+	−	+	NP
5	−	−	+	−	+	NP
6	−	−	+	−	+	NP
7	−	−	−	−	−	NP
8	−	−	−	+	−	NP
9	NP	NP	+	NP	NP	+
10	NP	NP	+	NP	NP	+
11	−	−	+	−	NP	+

FISH fluorescence in situ hybridization, *NP* not performed, *IHC* immunohistochemistry, *RT-PCR* Reverse transcription polymerase chain reaction, l*rHPV* = low-risk human papillomavirus, h*rHPV* high-risk human papillomavirus

HPV-associated compared to the remaining patients. In our study, the prognosis was actually quite favorable. This may not be a surprise as most patients had high- or low-risk HPV-associated tumors, arose from an existing sinonasal papilloma, or had *DEK::AFF2* fusion [19, 20, 22] and bland morphology, all of which have been associated with more favorable survival compared to conventional sinonasal SCC[17, 25–27].

Overall, our findings in AdSCC match well with sinonasal tract SCC in general, with a predilection for the nasal cavity, frequent smoking association, a significant fraction of high-risk HPV, and rare cases associated with sinonasal papillomas, low-risk HPV, or *DEK::AFF2* fusion [17, 25]. This small series, somewhat opposed to prior data on head and neck

AdSCC, found quite favorable prognosis, probably due to the high fraction of high-risk HPV-associated patients.

Conclusion

In summary, this series of sinonasal AdSCC helps define the morphology and genetic drivers of tumor growth. These drivers are similar to conventional sinonasal SCC and support that it is considered a histologic subtype of SCC, although it does appear that AdSCC is more frequently HPV associated, either high or low risk. The presence of established driver events that match conventional
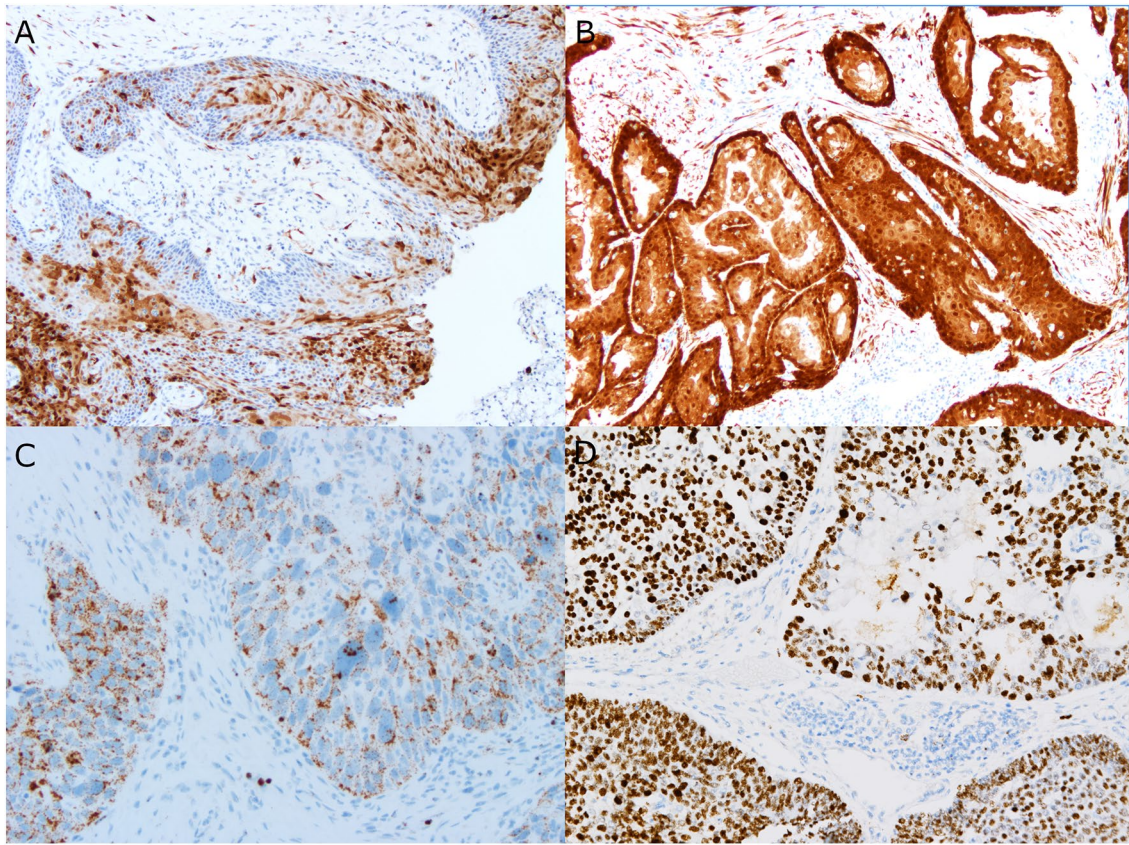
Fig. 5 Immunohistochemical and in situ hybridization studies showing positive cases for each of the genetic drivers or surrogate markers. **A** A high-risk HPV-independent AdSCC showing only patchy nuclear and cytoplasmic expression of p16 (below the 70% cut-off). **B** A high-risk HPV-associated AdSCC with strong, diffuse nuclear and cytoplasmic p16 expression. **C** A low-risk HPV-associated AdSCC showing punctate, granular brown nuclear and cytoplasmic staining by RNA in situ hybridization. **D** AFF2 immunohistochemistry on the single DEK::AFF2 fusion-positive AdSCC showing strong nuclear brown staining in almost all tumor cells and including many of the tumor cells forming glands

SCC along with the lack of *MAML2* translocation in any of our cases argues strongly that these tumors are not a type of salivary gland tumor.

Declarations

never contacted, and we did not require informed consent or specific consent to publish.

Consent to Participate Not applicable.

Consent for publication Not applicable.

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