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CASE REPORT

Dedifferentiated Salivary Hybrid Carcinoma of the Maxillary Sinus with Pagetoid Spread to the Overlying Lining Mucosa

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Introduction

Hybrid carcinoma of salivary glands is a very rare subtype of malignant salivary gland neoplasm with a little more than 30 cases documented in the literature [1–20] (See Table 1). Most cases of hybrid carcinoma of salivary glands have been reported in the parotid gland and palate. To date, only a single case of salivary hybrid carcinoma has been observed in the maxillary sinus [14]. Although dedifferentiation/high grade transformation has been described in a variety of malignant salivary gland tumors, this phenomenon has not been reported in salivary hybrid carcinoma [21, 22]. Furthermore, while pagetoid spread of neoplastic cells from a malignant salivary gland tumor to the overlying lining mucosa has been documented in the oral mucosa [21–23], such an incidence has not been reported in the maxillary sinus. Herein, we describe an additional case of hybrid carcinoma of salivary glands in the maxillary sinus that demonstrated simultaneous occurrence of high-grade transformation and intraepithelial pagetoid spread to the overlying sinus mucosa. This rarely reported phenomenon is not only of academic interest but can also pose significant diagnostic difficulties, particularly in distinguishing from a HPV-related carcinoma with adenoid cystic-like features.

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Case Report

A 68-year-old male patient was admitted to our hospital with the clinical presentation of a mass in the left maxillary sinus. A previous biopsy performed at an outside institute was diagnosed as squamous cell carcinoma involving a polyp originating in the left maxillary sinus. His clinical history was otherwise significant for hypertension, diabetes mellitus, and coronary artery disease.

In May 2013, the patient underwent partial maxillectomy including complete removal all mucosa from the left maxillary sinus as well as the anterior skull base. Secondary to positive surgical margins, a complete maxillectomy and partial resection of the hard palate with left osteocutaneous radial forearm flap was performed in July 2013, followed by radiation therapy. In May 2014, the patient developed lymphadenopathy of the left neck consistent with nodal metastasis. A left neck dissection were performed in June 2014 revealing two positive level II lymph nodes.

The partial maxillectomy was composed of a $4.5 \times 4 \times 1.1$ cm aggregate of multiple fragmented pieces of erythematous, pink-grey soft tissue resembling mucosa, partially covering cartilage and bone. The microscopic sections exhibited a peculiar interplay of morphologies: the majority of the tumor displayed typical morphologic features of an adenoid cystic carcinoma characterized by a dual population of relatively low-grade, monotonous basaloid myoepithelial and eosinophilic cuboidal ductal cells arranged in cribiform, solid, and tubular architectures. Basophilic mucoid and collagenous eosinophilic material was observed in the pseudocytsic spaces of the cribiform tumor nests (See Fig. 1a). The adenoid cystic carcinoma comprised approximately 50 % of the total mass. In addition, 20 % of the tumor exhibited distinct areas of solid

Table 1 Reports of hybrid salivary gland carcinomas

Case	References	Age	Sex	Site	Maximal size (cm)	Histologic patterns
1	[1]	53	M	R parotid	6	Acinic cell carcinoma–salivary duct carcinoma
2	[1]	67	F	L palate		Epithelial-myoepithelial carcinoma–adenoid cystic carcinoma
3	[2]			R parotid	2.5	Epithelial-myoepithelial carcinoma–adenoid cystic carcinoma-basal cell carcinoma
4	[3]	67	M	Parotid	3	Salivary duct carcinoma–myoepithelial carcinoma
5	[4]	67	F	L parotid	5.5	Salivary duct carcinoma–myoepithelial carcinoma
6	[5]	51	M	Palate	4.5	Acinic cell carcinoma–mucoepidermoid carcinoma
7	[29]	62	F	Parotid	3	Adenoid cystic carcinoma–salivary duct carcinoma
8	[7]	53	M	L Parotid	6	Epithelial-myoepithelial carcinoma–adenoid cystic carcinoma
9	[7]	71	M	R parotid	2.9	Adenoid cystic carcinoma–mucoepidermoid carcinoma
10	[7]	28	M	L parotid	2.5	Epithelial-myoepithelial carcinoma–adenoid cystic carcinoma
11	[7]	51	M	L palate	3.5	Epithelial-myoepithelial carcinoma–salivary duct carcinoma
12	[8]	36	F	Submandibular	3.5	Adenoid cystic carcinoma–salivary duct carcinoma
13	[9]	58	F	Parotid	2.5	Adenoid cystic carcinoma–salivary duct carcinoma
14	[10]	78	M	R parotid	4.5	Epithelial-myoepithelial carcinoma–mucoepidermoid carcinoma
15	[11]	74	F	R parotid	10	Adenoid cystic carcinoma–salivary duct-acinic cell-low grade polymorphous Ca
16	[11]	56	F	L parotid	2	Epithelial-myoepithelial carcinoma–basal cell adenocarcinoma
17	[11]	73	M	L parotid	2	Epithelial-myoepithelial carcinoma–basal cell adenocarcinoma
18	[11]	40	F	R parotid	3	Epithelial-myoepithelial carcinoma–keratinizing SCC
19	[11]	81	M	R submandibular	3	Adenoid cystic carcinoma–salivary duct carcinoma
20	[11]	65	F	R parotid	5	Adenoid cystic carcinoma–salivary duct carcinoma
21	[11]	42	M	L parotid	4	Myoepithelial carcinoma–salivary duct carcinoma
22	[11]	65	M	R parotid	3.5	Adenoid cystic carcinoma–salivary duct carcinoma
23	[11]	64	M	R lacrimal	5	Salivary duct carcinoma–keratinizing SCC
23	[12]	49	F	L palate	3.5	Adenoid cystic carcinoma–mucoepidermoid carcinoma
24	[12]	71	M	R Palate	4	Epithelial-myoepithelial carcinoma–adenoid cystic carcinoma
26	[13]		F	Parotid	4	Epithelial-myoepithelial carcinoma–lymphoepithelial carcinoma
27	[14]	26	F	R maxillary sinus		Epithelial-myoepithelial carcinoma–adenoid cystic carcinoma
28	[15]	68	F	R parotid	4	Adenoid cystic carcinoma-basal cell carcinoma
29	[16]	65	M	Upper lip	3 × 2.5	Epithelial-myoepithelial carcinoma–adenoid cystic carcinoma
30	[17]	74	M	R parotid		Epithelial-myoepithelial carcinoma–salivary duct carcinoma
31	[19]	78	M	R submandibular		Epithelial-myoepithelial carcinoma–adenoid cystic carcinoma
32	[18]	53	M	Larynx		Adenoid cystic carcinoma–adenocarcinoma, NOS
33	[20]	59	F	L sublingual	1.7	Adenoid cystic carcinoma–salivary duct carcinoma
34	This report	68	M	L maxillary sinus	6.5	Epithelial-myoepithelial carcinoma–adenoid cystic carcinoma
Summary		60 ± 14 (26–81)	14F:20M	71 % major SG 29 % minor SG	3.9 ± 1.7 (1.7–10)	59 % Adenoid cystic carcinoma; 47 % Epithelial-myoepithelial carcinoma; 44 % Salivary duct carcinoma; 12 % Mucoepidermoid carcinoma and basal cell adenocarcinoma; 9 % Acinic cell carcinoma; 6 % myoepithelial carcinoma & squamous cell carcinoma; 3 % Adenocarcinoma NOS, low grade polymorphous carcinoma

L left, *R* right, *SG* salivary gland

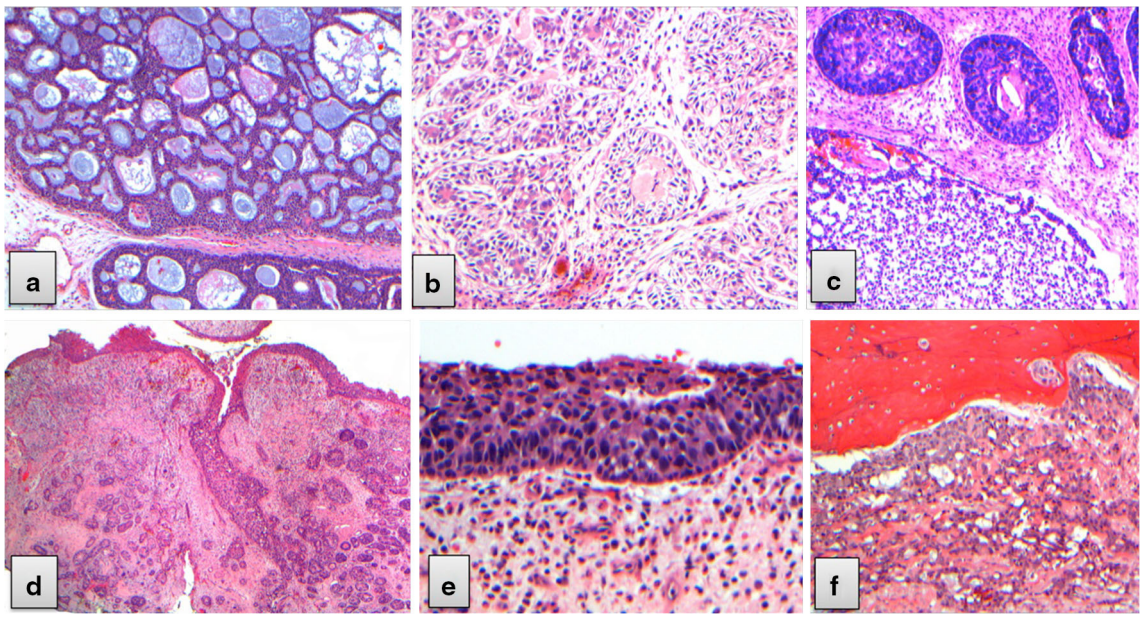

Fig. 1 **a–f** Salivary hybrid carcinoma composed of adenoid-cystic carcinoma (**a**) and epithelial-myoepithelial carcinoma (**b**) with foci of high-grade transformation (**c**). High-grade transformed neoplastic cells expand a secretory duct opening to the surface epithelium (**d**) leading to pagetoid spread of tumor cells in the lining mucosa (**e**). Bone invasion by high-grade adenocarcinoma in the re-excision (**f**)

nests and tubules of polygonal myoepithelial cells with clear cytoplasm in the periphery and central cuboidal eosinophilic ductal cells consistent with an epithelial–myoepithelial carcinoma (See Fig. 1b). The third component of the tumor was composed of high-grade polygonal eosinophilic neoplastic cells that displayed pleomorphic, vesicular nuclei and scattered prominent nucleoli. The high-grade neoplastic cells were arranged either as distinct solid nests (See Fig. 1c) or intimately intermingled with the basaloid cells within the nests of the adenoid cystic carcinoma. Notably, this high-grade component focally filled and expanded superficial ducts that opened directly to the overlying lining mucosa (See Fig. 1d). The surface epithelium was also infiltrated by the high-grade neoplastic cells in a pagetoid spread pattern (See Fig. 1e). The high-grade neoplastic cells were predominantly identified in the upper levels of the surface epithelium, sparing the basal layer of the lining mucosa.

Immunohistochemical studies with a panel of antibodies demonstrated a diverse immunohistochemical-staining pattern between the different neoplastic components as illustrated in Table 2, which supported the spectrum of histologic differentiation in this tumor. Notably, most of the solid nests of high-grade neoplastic cells were surrounded by an intact layer of p63 positive myoepithelial layer (See Fig. 2a),indicative of their predominantly intraductal/in situ growth. In addition, there were significant differences in the expression of Ki-67, p53, and Her2-neu in the high-grade neoplastic cells compared to the low grade components of adenoid cystic carcinoma and epithelial-myoepithelial carcinoma (See Fig. 2b–f). Overall, the histologic and immunohistochemical findings were consistent with those of a salivary hybrid carcinoma

Table 2 Tumor immunophenotypes

Immunostains	ACC	Epi.Myo.CA	High grade T
CKAE1/AE3	++	duct:++, myo: ±	++
CK5/6	++	+	Mostly −
Cam 5.2	++	++	++
MOC-31	–	–	++
p63	peri: ++, cent.: −	duct: −, myo: ++	–
SMA	peri: +, cent: −	duct: −, myo: +	–
S-100	peri: +, cent: −	duct: +, myo: −	–
CD117	++	+	–
p16	peri: +, cent.: −	duct: +, myo: −	–
ER	–	–	–
PR	–	–	–
GCDFP-15	–	–	–
p53	–	–	80–90 % +
Ki-67	10 % +	10 %	100 % +
Her2-neu	–	–	Focally +
Androgen receptor	–	–	–

ACC adenoid-cystic carcinoma, *Epi.Myo. CA* epithelial-myoepithelial carcinoma, high grade, *T* high-grade transformation, *SMA* smooth muscle actin, *peri* peripheral cells, *cent* centrally located cells, *myo* myoepithelial cells, *duct* ductal cells

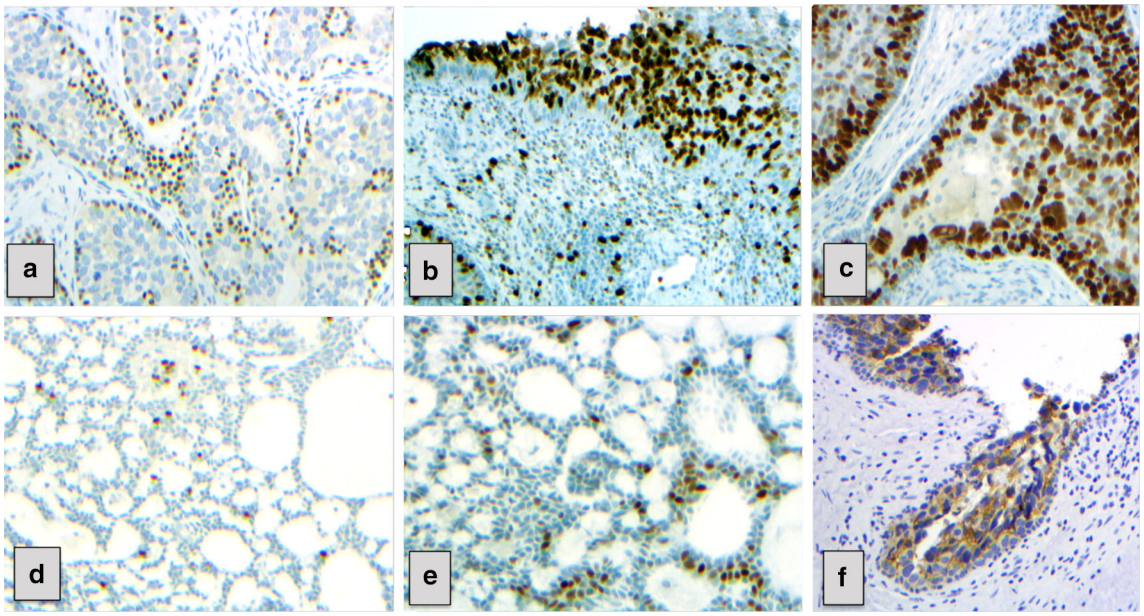

Fig. 2 **a**–**f** Immunohistochemical studies display a layer of p53 positive myoepithelial cells at the periphery of the nests of transformed neoplastic cells (**a**). There is a significantly higher expression of Ki-67 (**b**) and p53 in the high grade component (**c**) compared to the adenoid-cystic carcinoma (**d**, **e**). Focal Her2-neu immunopositivity in the high-grade component (**f**) whereas the low grade adenoid-cystic carcinoma is completely negative (not shown)

composed of adenoid cystic and epithelial-myoepithelial carcinoma, associated with high-grade transformation and pagetoid spread in the lining epithelium.

The re-excision showed predominantly residual adenoid cystic carcinoma and scattered foci of invasive high-grade adenocarcinoma. Interestingly, whereas the adenoid cystic component was mostly confined within the stroma of the respiratory mucosa, the high-grade adenocarcinoma primarily invaded the underlying bone (See Fig. 1f), indicative of the aggressive nature of this component. The lining mucosa still demonstrated focal involvement by high-grade carcinoma in a pagetoid spread pattern. A residual component of epithelial-myoepithelial carcinoma was not identified. The left neck dissection performed 1 year later demonstrated two positive lymph nodes harboring high grade adenoid cystic carcinoma.

To evaluate the possibility of high-risk HPV infection, in situ hybridization was performed utilizing primers that can detect high risk HPV genotypes (i.e. 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 66) (methods previously described by Carlson et al. [24]). By in situ hybridization, no high-risk HPV DNAs were detected in any components of the tumor.

Discussion

First described by Seifert in 1996 [1], hybrid tumor of salivary glands is defined as "very rare tumor entities which are composed of two different tumor entities, each of which conforms with an exactly defined tumor category. The tumor entities in a hybrid tumor are not separated but have an identical origin within the same topographical area". Hybrid tumors of the salivary glands are rare, accounting for less than 0.1 % of all salivary gland neoplasms. If only pure malignant hybrid tumors of salivary glands (all histologic components of the hybrid tumor are malignant) are considered, analysis of the literature revealed 34 cases [1–20] in the head and neck area, including the current case (see Table 1). Hybrid carcinomas of salivary glands commonly occur in older patients with a mean age of 60 years (range 26–81 years) with a slight male sex prevalence (20 males: 14 females). The most common sites of origin are the parotid gland (60 %) and palate (15 %). Other rare primary sites are the submandibular salivary gland, maxillary sinus, sublingual salivary gland, upper lip, lacrimal gland, and larynx. As the name implies, a broad range of histologic subtypes are reported in hybrid carcinomas, ranging from adenoid cystic carcinoma, epithelial-myoepithelial carcinoma, salivary duct carcinoma, basal cell carcinoma, myoepithelial carcinoma, mucoepidermoid carcinoma, lymphoepithelial carcinoma, to polymorphous low-grade adenocarcinoma, with the majority (94 %) of the cases exhibiting a combination of 2 subtypes. The most commonly reported carcinomatous components are adenoid cystic carcinoma (59 %), epithelial-myoepithelial carcinoma (47 %), and salivary duct carcinoma (44 %). The most common combinations are epithelial-myoepithelial

carcinoma with adenoid cystic carcinoma (24 %, 8/34) and adenoid cystic carcinoma with salivary duct carcinoma (20 %, 7/34). Herein, we report a hybrid carcinoma of salivary glands arising in the maxillary sinus composed of adenoid cystic carcinoma and epithelial-myoepithelial carcinoma and showing areas of high-grade transformation and pagetoid spread to the overlying mucosa. The present case appears to be unique for several features.

First, this is only the second case of hybrid carcinoma of salivary glands in the maxillary sinus, but the first de novo hybrid carcinoma of salivary glands in this region. To date, there is only a single another case of hybrid carcinoma in the maxillary sinus [14]. The patient was a 26 year-old female who developed a hybrid carcinoma of epithelial-myoepithelial carcinoma and adenoid cystic carcinoma in the right maxillary sinus, a similar histopathology as our case. Of note, the patient had surgery for a pleomorphic adenoma at the same site 2 years before so that the hybrid carcinoma in that case probably represented a carcinoma ex pleomorphic adenoma. In contrast to that case, the hybrid carcinoma in the current case did not show any evidence of a preexisting or concurrent benign or low grade conventional salivary gland neoplasm that could potentially serve as a precursor.

Secondly, dedifferentiation or the nowadays preferable term high grade transformation has been described in various primary salivary gland tumors such as acinic cell carcinoma, adenoid cystic carcinoma, epithelial-myoepithelial carcinoma, low-grade mucoepidermoid carcinoma, polymorphous low-grade carcinoma, myoepithelial carcinoma, hyalinizing clear cell carcinoma [25], and most recently the mammary analogue secretory carcinoma [26]. However, this phenomenon has not been documented in salivary hybrid carcinomas. Admittedly, it is rather controversial how to classify the current tumor. In the original seminal paper by Seifert et al. [1] on salivary hybrid carcinomas, one hybrid carcinoma composed of epithelial-myoepithelial and adenoid cystic carcinoma was included in their series. Since then, a total of 8 additional hybrid carcinomas displaying this combination have been reported in the literature. However, Grenko et al. [27] described in 1998 three cases of adenoid cystic carcinoma with epithelial-myoepithelial carcinoma-like foci and two epithelial-myoepithelial carcinomas with adenoid cystic carcinoma-like areas. In view of the immunohistochemical and ultrastructural similarities in the adenoid-cystic and epithelial-myoepithelial components, the authors were of the opinion that the differences in these tumors merely represent the same process of both ductal and myoepithelial differentiation, only in variable proportions to generate a range of morphologic heterogeneity. Therefore, the authors believed that a salivary gland tumor displaying both adenoid cystic and epithelial-myoepithelial carcinoma should not be categorized as a hybrid carcinoma, but rather classified according to the most dominant component. Interestingly, no salivary hybrid carcinoma composed of adenoid-cystic carcinoma and epithelial-myoepithelial carcinoma was described in the largest series of hybrid carcinoma, although this biphasic divergence is the most common combination documented in salivary hybrid carcinomas [11]. It is unclear whether the authors excluded hybrid carcinomas with this combination from their series or they did not encounter such form of hybrid carcinomas in their files. Since a combination of adenoid cystic and epithelial-myoepithelial carcinoma is the most common subtype of salivary hybrid carcinoma reported in the literature (see Table 2), these tumors appear to be a legitimate form of salivary hybrid carcinoma. Hence, we regarded the current neoplasm a salivary hybrid carcinoma exhibiting high-grade transformation. Nevertheless, we acknowledge that some pathologists might prefer to classify our case as an adenoid cystic carcinoma with epithelial-myoepithelial carcinoma-like areas and high grade transformation.

Finally, the growth pattern of the high-grade component in the current case is rather unique compared to other dedifferentiated salivary gland tumors described in the literature. Whereas the dedifferentiated component of most salivary gland carcinomas with high-grade transformation exhibit an infiltrative growth, our high-grade transformed cells appear to grow predominantly in an intraductal pattern as immunohistochemical studies demonstrated an intact layer of myoepithelial cells in most of the nests of high-grade carcinoma. In many nests, the high-grade tumor cells intermingled intimately with the adenoid cystic carcinoma cells. There were only rare microscopic foci of infiltrative high-grade adenocarcinoma invading the underlying bone. The prevalent intraductal growth of the high-grade carcinoma most likely facilitated the pagetoid spread of the tumor cells to the overlying lining mucosa as dilated secretory ducts filled with high-grade tumor cells were seen opening directly into the epithelial surface. Pagetoid spread of neoplastic cells from a salivary carcinoma to the lining mucosa is a relatively rare phenomenon with only 3 cases previously described in the literature. In the first case, pagetoid spread of an underlying poorly differentiated adenocarcinoma to the tongue was described [21]. The illustrating photographs and histologic description were of such poor quality that a definitive classification of the adenocarcinoma was not possible. On the other hand, both recent cases demonstrated a salivary duct carcinoma with an intraductal growth of the tumor cells in addition to the invasive component [22, 23]. It was postulated that the dearth of pagetoid spread from salivary gland tumors to the lining mucosa is related to the rare incidence of extensive intraductal growth of these tumors

[22]. In this regard, our case appears to provide further evidence to this hypothesis; however, additional cases need to be studied before any definitive generalizations can be made.

In regards to differential diagnosis, this hybrid carcinoma of salivary glands can be easily misinterpreted as a human papillomavirus-related carcinoma with adenoid cystic-like features due to the intraepithelial pagetoid spread of the neoplastic cells and the presence of an adenoid cystic carcinoma component in the tumor. HPV-related carcinoma with adenoid cystic-like features is a recently described peculiar variant of head and neck cancer restricted to the sinonasal tract with the invasive component exhibiting morphologic similarities to an adenoid cystic carcinoma [28]. The overlying mucosa commonly demonstrates squamous dysplasia/carcinoma in situ which is diffusely positive for p16. The pagetoid spread of this hybrid carcinoma in the overlying mucosa may impart the impression of dysplastic changes or carcinoma in situ. In contrast to the more common squamous dysplasia, the neoplastic cells in this hybrid carcinoma were polygonal with abundant eosinophilic cytoplasm and vesicular nuclei and did not involve the basal layer of the lining mucosa. As a matter of fact, the tumor cells spared the basal layer and could be seen clearly above the uninvolved basal layer contrary to squamous dysplasia in which the dysplastic process generally starts at the level of the basal layer. Furthermore, the intraepithelial pagetoid tumor cells of this hybrid carcinoma were positive for MOC-31 but negative for p63 and Cytokeratin 5/6, thus supporting the adenocarcinomatous nature of the neoplastic cells and arguing against a squamous dysplastic process. Lastly, HPV in situ hybridization and immunohistochemical studies with p16 testing were negative in the intraepithelial neoplastic cells. Because only a small number of cases of HPV-related carcinoma with adenoid cystic-like features with any significant follow-up data have been published so far, it is unclear whether the distinction between these 2 rare types of carcinomas in the maxillary sinus would have any clinical implication although hybrid carcinomas of salivary glands or salivary gland carcinoma with high grade transformation are generally regarded as aggressive tumors.

Conclusion

In summary, we have described a novel case of salivary hybrid carcinoma in the maxillary sinus. The tumor was not preceded by any preexisting benign conventional salivary tumor and demonstrated high-grade transformation, a previously not described incidence in this tumor type. Owing to the extensive intraductal growth of the high-grade component, the tumor was associated with widespread pagetoid spread of the neoplastic cells on the surface mucosa, which could potentially be confused for a dysplastic process. Awareness of this phenomenon is important for pathologists to avoid misdiagnosing this rare type of salivary gland tumor for a variant of HPV-related carcinoma of the sinonasal tract.

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Conflict of interest None.

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