Anaplastic Myoepithelial Carcinoma of the Sinonasal Tract: an Underrecognized Salivary-Type Tumor Among the Sinonasal Small Round Blue Cell Malignancies? Report of One Case and a Review of the Literature

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Abstract We present a 45 year old female patient with a nasal carcinoma showing high-grade/anaplastic histomorphological features and with a distinct myoepithelial immunohistochemical phenotype including positivity for smooth muscle actin, p63, S100 protein with no sustentacular pattern, calponin, cytokeratin 14, vimentin and cytokeratins (AE1-3 and CK5/6). A minority (<5%) of the cells showed focal and variable immunoreactivity for EMA with no cuticular/canalicular pattern. Bcl-2, CD99, CD117 and CD56 were variously positive, but chromogranin and synaptophysin were negative. Weak to moderate nuclear p53 immunoreactivity was seen in 50% of tumor cells. Mib-1/Ki-67 showed an average proliferation of 60–70%. Fluorescent in situ hybridization revealed no *EWS*-gene translocation. In situ hybridization for EBER was negative.

Keywords Anaplastic · High-grade · Myoepithelial · Carcinoma · Sinonasal · Small round blue cell tumor · Salivary gland

Introduction

The sinonasal tract is an anatomic location where a range of different malignant small round blue cell tumors of various histogenesis and with different degrees of

biological malignancy may originate. Herein, we present the clinicopathological features of a tumor that showed undifferentiated/anaplastic cyto- and histomorphological features, but with a distinct myoepithelial phenotype on immunohistochemistry. We label the tumor as an anaplastic myoepithelial carcinoma. We are not aware of any similar published tumor in this location and as such this tumor should be included in the list of diagnostic possibilities to be considered in the frequently complex differential diagnostic work up of sinonasal malignant small round blue cell tumors, a group of biologically diverse tumors with overlapping morphologic features.

Materials and Methods

The tissue was fixed in formalin, embedded in paraffin and 4 µm thin sections were cut and stained with Hematoxylin and Eosin. Immunohistochemistry (IHC) using the primary antibodies as listed in Table 1 was performed, using the Roche Ventana BenchMark XT autostainer and Ventana Ultra View Universal DAB Detection kit, with appropriate positive controls.

In situ hybridization for EBV-encoded small RNAs (EBER) was performed with Leica BondMax autostainer using Leica Bond Polymer Detection kit.

Fluorescent in situ hybridization (FISH) to detect *EWS* (22q12) gene rearrangement utilizing Vysis LSI *EWSR1* Dual Color, Break Apart rearrangement probe was employed to exclude Ewing's sarcoma. Five micrometer sections of formalin-fixed, paraffin-embedded tissue were pre-treated and subjected to protease digestion. The cells and probes were incubated at 37 degrees Celsius overnight using the ThermoBrite denaturation/hybridization system (Vysis, Downer's Grove, IL, USA). At least 100

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Table 1 Antigens/clones/dilutions and retrieval methods used in the immunohistochemical study

Antigen	Clone	Dilution	Antigen retrieval	Supplier
SMA	1A4	1:1,000	CC1-mild (30')	DAKO
Vimentin	V9	1:3,000	CC1-mild (30')	DAKO
AE1/3	AE1/3	1:300	Protease 2–8'	DAKO
CK5/6	D5/16 B4	1:50	CC1-standard (60')	DAKO
CK14	Polyclonal	1:100	CC1-standard (60')	Neomarker
p63	4A4	1:300	CC1-standard (60')	DAKO
S100	Polyclonal	1:2,000	No retrieval	DAKO
EMA	E29	1:200	CC1-mild (30')	DAKO
Myogenin	F5D	1:1,000	M/W pH 9 for 20'	DAKO
Desmin	D33	1:100	CC1-mild (30')	DAKO
Bcl2	124	1:50	CC1-standard (60')	DAKO
CD117	Polyclonal	1:200	CC1-standard (60')	DAKO
CD56	1B6	1:50	CC1-standard (60')	Novocastra
Chromogranin	Polyclonal	1:800	CC1-short (8')	DAKO
CD99	12E7	1:200	CC1-mild (30')	CD99
Synaptophysin	Polyclonal	1:100	CC1-mild (30')	Cell Marque
Melan A	A103	1:30	CC1-standard (60')	Novocastra
HMB45	HMB 45	1:100	CC1-mild (30')	Novocastra
Ki-67	MIB 1	1:50	CC1-mild (30')	DAKO
p53	DO-7	1:100	CC1-standard (60')	DAKO
Her2	4B5	RTU	CC1-mild (30')	Roche

SMA smooth muscle actin, CC1 Cell Conditioning solution pH6, M/W microwave, RTU ready to use

Except for calponin and myogenin which were performed manually, the other IHC markers were performed using Roche Ventana BenchMark XT autostainer and with Ventana Ultra View Universal DAB Detection kit

non-overlapped nuclei with distinct signals were scored by two independent observers and the interpretation of intact and split signals was based on generally accepted guidelines recommended by Vysis. Positive result is defined as 15% or more of cells with split signals of more than 1 signal diameter apart.

Case Report

The patient is a non-smoking female, 45 years who presented with right epistaxis and nasal obstruction for 6 and 3 months, respectively. On clinical examination an expansile mass was seen occupying the entire right anterior nasal space. Magnetic resonance imaging (MRI) showed a $5.4 \times 2.8 \times 3.9$ cm expansile lobulated mass involving the right nasal cavity (middle turbinate) and ethmoid cells. The lamina papyracea and medial orbital wall were deficient. However, no definitive invasion of the mass into the right maxillary sinus or orbit was noted. Superiorly the tumor occluded the right frontoethmoidal recess (Fig. 1). Posteriorly, it bulged into the right posterior nasal cavity. No intracranial extension was noted. Posteriorly, the tumor reached the right sphenopalatine foramen. No extension into the nasopharynx was present and the parapharyngeal space was clear. Two biopsies, performed under topical anaesthesia in the outpatient clinic, yielded mostly necrotic tissue with only small amounts of viable neoplastic tissue. A third biopsy was performed under general anaesthesia

and this resulted in large amounts of viable tumor. Subsequently, she underwent a craniofacial resection, removing the residual tumor and clearance of margins. The patient is currently receiving adjuvant radiotherapy. The

Fig. 1 An MRI-scan showed an expansile lobulated tumor involving the right nasal cavity. No definitive invasion of the mass into the right maxillary sinus or orbit was noted

Fig. 2 Imprint preparations from the tumor showed abundant cohesive clusters of malignant cells with pleomorphic, hyperchromatic nuclei featuring high nuclear to cytoplasmic ratio (**a**) and presence of metachromatic stroma (**b**)

case was recently diagnosed, precluding any meaningful follow-up.

Results

Routine Morphology

Imprint preparations from the tumor showed abundant cohesive clusters of malignant cells with pleomorphic, hyperchromatic nuclei featuring high nuclear to cytoplasmic ratio and presence of metachromatic stroma (Fig. 2).

On histological examination, in addition to large confluent necrosis, the tumor displayed neoplastic cells in sheets and lobular configurations (Fig. 3A). The lobules were separated by edematous connective tissue with weakly basophilic mucin and/or hyalinized stroma. Neoplastic cells were mostly epithelioid but in multiple areas, spindling of tumor cells was seen (Fig. 3B). The malignant cells had

high nuclear to cytoplasmic ratio, fine chromatin and small to inconspicuous nucleoli. In some areas the cytological atypia was aggravated, i.e. the size of the nuclei was increased, the chromatin was coarser and larger nucleoli were present (Fig. 3C). Numerous mitotic figures (up to 10/HPF) including atypical mitotic figures as well as prominent apoptotic activity were present. In areas where the neoplastic cells showed a more spindled morphology, more abundant basophilic extracellular matrix was present. No basement membrane material was seen and the cells contained no intracellular mucin. Varying numbers of pseudolumina were present, but no true ductular differentiation was discerned (Fig. 3D). No clear- or plasmacytoid cells or collagenous crystalloids/spherules were present. The whole tumor displayed these high-grade features and no well differentiated tumor component was present.

Immunohistochemistry

Neoplastic cells revealed a myoepithelial phenotype with diffuse and strong positivity for smooth muscle actin (SMA) in 80% of neoplastic cells (Fig. 4A), p63 (diffuse, mostly moderate intensity in 50% of cells), (Fig. 4B) and focal, frequently both strong nuclear and cytoplasmic staining for S100 protein (Fig. 4C). No sustentacular pattern was present. Strong immunoreactivity for calponin and cytokeratin 14 was seen in 50% of tumor cells (data not shown). Scattered tumor cells were positive for GFAP. The majority of cells were also immunoreactive for vimentin and cytokeratins; AE1-3 and CK5/6 (Fig. 4D, E). A minority (<5%) of the cells showed focal and variable immunoreactivity for EMA with no cuticular/canalicular pattern (data not shown). Both Bcl-2 and CD117 showed moderate to strong diffuse expression (data not shown). There was also diffuse positivity for CD99 including both cell membrane and cytoplasmic immunoreactivity (data not shown). CD56 was widely positive with weak to moderate intensity (data not shown). Chromogranin and synaptophysin, Melan A, HMB-45, myogenin and desmin were negative. Weak to moderate nuclear p53 immunoreactivity was seen in 50% of tumor cells (Fig. 4F). Mib-1/Ki-67 showed an average proliferation of 60–70% with areas where >80% of tumor cells were positive for this proliferation marker (Fig. 4G).

Flourescent in situ hybridization study revealed no *EWS*-gene translocation. In situ hybridization for EBER was negative.

Discussion

Small round cell tumors arising in the sinonasal tract comprise a heterogenous group of malignant tumors. Herein

Fig. 3 Hematoxylin and eosin stained sections showing the tumor growing in nests and sheets under the nasal mucosa (a). Neoplastic cells displayed focal spindling (b). Areas with neoplastic cells

featuring increased nuclear size and atypia including coarse chromatin and prominent nucleoli were present (c). Pseudolumina were seen, but no true ductular differentiation was discerned (d)

we characterize a tumor that adds itself to the list of neoplasms that should be considered when faced with a malignant sinonasal neoplasm composed of small round blue cells—an anaplastic myoepithelial carcinoma. Anaplastic/undifferentiated malignant tumors of the sinonasal tract have recently been reviewed by Wenig [1]. Confronted with a biopsy composed of small round blue cells with malignant histological features (i.e. neoplastic cell with no definitive organoid differentiation, high nuclear to cytoplasmic ratio, high mitotic and apoptotic activity, necrosis), the differential diagnosis includes a whole range of entities such as sinonasal undifferentiated carcinoma (SNUC), small cell neuroendocrine carcinoma (SNEC), nasopharyngeal type of undifferentiated carcinoma (NPUCA), high-grade olfactory neuroblastoma (HG-ONB), primitive neuroectodermal tumor/Ewing sarcoma (PNET/ES), small cell and basaloid squamous cell carcinoma (SCSCC/BSCC), NUT-translocated carcinoma, desmoplastic small round cell tumor (DSRCT), alveolar rhabdomyosarcoma (ARMS), malignant melanoma, neuroepithelial (“neuroblastoma-like”) elements in a sinonasal teratocarcinosarcoma (SNTCS), metastatic neuroblastoma (children), solid and dedifferentiated variants of adenoid cystic carcinoma (ADCC-S/D) and hematolymphoid malignancies such as extranodal nasal NK-/T-cell lymphoma, aggressive B-cell lymphomas and myeloid sarcoma/chloroma. An adequate biopsy and a

comprehensive immunohistochemical study and, in selected cases, in situ hybridization for EBER and molecular genetic studies to detect translocations characteristic of PNET/ES, DSRCT and ARMS would resolve most of these differential diagnostic issues. Importantly, it should be emphasized that membranous expression of CD99, although highly sensitive for PNET/ES, lacks specificity and has been reported in other small round blue cell tumors, such as rhabdomyosarcoma, some carcinomas, lymphoblastic lymphomas, neuroendocrine tumors, DSRCT and mesenchymal chondrosarcoma. The possibility of a SNUC was given serious consideration in the diagnostic work-up of our case. In the review article on SNUC by Ejaz and Wenig, the authors state that immunoreactivity for CK5/6 and CK14 have reportedly been negative and immunoreactivity for mesenchymal markers like vimentin and muscle markers including actins are usually negative [2]. In our case 80% of tumour cells were strongly positive for SMA, the majority of tumor cells were immunoreactive for vimentin and CK5/6, and 50% of the neoplastic cells were positive for CK14. This immunoprofile argues strongly against the possibility of a SNUC. We also contemplated the possibility of a carcinoma ex pleomorphic adenoma (PA), but the absence of a long history of local symptoms and no remnants of a PA in the resected specimen are not consistent with this. The tumor did not show the multiple small well demarcated squamoid foci that are

Fig. 4 Photomicrographs from the immunohistochemical study showing strong and diffuse reactivity for smooth muscle actin (**a**). Fifty percentage of tumor cells displayed nuclear positivity for p63 with no peripheral pattern (**b**). Strong nuclear and cytoplasmic positivity for S-100 protein with no sustentacular pattern was present (**c**).

Immunoreactivity for cytokeratins; AE1-3 (**d**) and CK5/6 (**e**) was present in the majority of tumor cells. Moderate nuclear reactivity for p53 was present in 50% of tumor cells (**f**). The nuclear positivity for Mib-1/Ki-67 was high with areas showing >80% proliferative activity (**g**)

characteristic of a NUT-translocated carcinoma. No areas of keratinization, no squamous dysplasia in the overlying epithelium, no reduplicated basement membrane material, the presence of metachromatic stroma and most importantly the immunohistochemical profile are features that are not consistent with a small cell/basaloid variant of squamous cell carcinoma.

Myoepithelial carcinoma (MECA) is an uncommon salivary gland neoplasm which occurs over a wide age range, most commonly seen in the parotid gland, but also in the submandibular gland and minor salivary glands. The latter being the most frequently seen in the palate. Outside the major salivary glands and oral cavity, myoepithelial carcinomas are rarities. MECA was first included as an entity in the 1991 WHO classification of salivary gland tumors. This tumor may arise *de novo* or as secondary

progression from a pleomorphic adenoma or myoepithelioma. A range of histomorphological patterns (solid, trabecular, reticular, fascicular, dissociated) and cytological types (spindle, stellate, plasmacytoid, hyaline, clear cell and vacuolated, signet ring cell-like) have been recognized. Frequently these histological patterns and cell types are mixed within the same tumor. Myxoid and/or hyaline extracellular matrix in varying proportions (sparse to abundant) and necrosis are frequently present. Pseudocystic/pseudoluminal structures may be seen, but more than occasional true lumens should cast doubt on the diagnosis. According to the criteria specified in the 2005 WHO edition on Head and Neck tumors, “reactivity for cytokeratin and at least one of the other myoepithelial markers, including smooth muscle actin, GFAP, CD10, calponin, and smooth muscle heavy chain, is required for diagnosis”.

The histological grade varies. In a series of 25 MECAs of salivary glands by Saveria et al., 40% were considered high-grade [3]. There was a trend towards more aggressive clinical behavior in the high-grade than in the low-grade tumors. Although it should be noted that two patients with low-grade tumors developed metastasis, of which one patient succumbed to the disease. MECA have, besides the mammary gland, also been described in the nasopharynx [4, 5], lung [6], larynx [7, 8], the infratemporal fossa [9], orbit [10] and skin [11–13].

Myoepithelial neoplasms of the sinonasal tract are rare tumors. Only a few primary myoepitheliomas arising in this region have been published as isolated case reports [14–17]. To the best of our knowledge, only two cases of MECA in the sinonasal region (both located in the maxillary sinus) have previously been published [18, 19]. The patient presented by Graadt van Roggen et al. [18] was a 67 year old male and the tumor displayed “cells with round to spindly polymorphic nuclei...ample, generally acidophilic cytoplasm”. The tumor published by Hsiao et al. [19] (60 year old male) was a low-grade (no mitotic figures or nuclear pleomorphism), plasmacytoid MECA which spread to the brain and caused the demise of the patient 5 months after surgery. The first tumor showed strong positivity for S100 protein and cytokeratin, and focal positivity for vimentin and SMA, while the second case demonstrated S100 protein, actin and cytokeratin expression. No other immunohistological findings were reported. Histologically, these two reported cases are distinctly different from our case.

From a differential diagnostic point of view, our tumor should be distinguished from the solid and dedifferentiated variants of adenoid cystic carcinoma (ADCC-S/ADCC-D). The features of ADCC-S and ADCC-D in standard textbooks in Head and Neck Pathology and previously published cases (ADCC-D) are summarized in Table 2. From this review, it is apparent that the major standard text books have a slightly different approach to these issues. According to the 2005 WHO classification of Head & Neck tumors [20], true ducts are “invariably present” in the solid type of ADCC. However, no data on the immunohistochemical features of ADCC-S are presented. Cardesa and Slootweg [21] state (p. 148) that “Within the solid masses of tumor cells, there are small duct-like spaces surrounded by a definitive layer of epithelial cells”. As with the WHO, the immunophenotype of the cells in ADCC-S is not commented on. Wenig writes that ADCC-S shows “little tendency” to form ducts and the neoplastic cells tend to be larger and display greater nuclear pleomorphism and increased mitotic activity [22] whereas Gnepp states (p. 483) that the solid pattern of ADCC “consists of large islands of carcinoma composed predominantly of myoepithelial cells with infrequent true

lumina lined with cuboidal epithelial cell, with only occasional punctuation by pseudocysts” [23]. Specific immunohistochemical features of the “predominantly myoepithelial cells” are not further specified. Hence, it is difficult to understand why these cells should be myoepithelial, especially since the photomicrograph (Fig. 5.35) provided on ADCC-S, shows a rather uniform neoplastic population both surrounding and in between the luminal spaces present. The immunohistochemical features of ADCC-S has been reported on by Serrano et al. [24]. They found that p63 positive neoplastic cells were seen in the periphery of the cell nests, which is in contrast to the weak to moderate diffuse distribution of p63 positive cells in the case presented herein.

Except for Wenig [22] who stated that the phenomenon of dedifferentiation refers to “an unusual occurrence of a histologically low-grade ADCC transforming to a high-grade carcinoma and/or progression from solid ADCC to a high-grade carcinoma”, neither WHO, Cardesa and Slootweg nor Gnepp commented on ADCC-D. The histological features characterizing dedifferentiation are, according to Wenig, “the presence of necrosis, high mitotic rate and loss of biphasic ductal-myoeplithelial differentiation by light microscopy and loss or diminished p63 and calponin expression by immunohistochemistry”. Whether the latter is also a feature of ADCC-S is not explicitly stated, but the photomicrographs 18.63 from Wernig [22] and 5.35 in Cardesa and Slootweg [21] seem to suggest that this may be the case. In addition, according to WHO, “The solid or basaloid type is formed of sheets of uniform basaloid cells lacking tubular or microcystic formation”, implying that there is absence of biphasic ductal-myoeplithelial differentiation in ADCC-S. Nagao et al. studied six cases of ADCC-D and the dedifferentiated component in all cases were either a poorly differentiated or undifferentiated carcinoma with no expression of myoepithelial markers [25]. Similarly, Seethala et al. [26] reported a series of 11 ADCC with “high-grade transformation” and the high-grade components were histologically “poorly differentiated cribriform adenocarcinoma” or “undifferentiated solid carcinoma”. The paper was, however, unclear regarding the terminology of “high-grade” in the context of ADCC, and appears to include both ADCC-S and ADCC-D. There was also ambiguity in this paper regarding the preservation of myoepithelial differentiation in the transformed areas. According to Table 4, none of the dedifferentiated components appeared to show positive staining for p63, calponin or SMA. However, it was stated in the text that the myoepithelial component was “focally lost in the transformed areas of all cases, though there were still foci with incomplete staining for basal/myoepithelial markers even within these components”. The authors concluded that “the

Table 2 Summary of histological features and immunohistochemical findings of solid and dedifferentiated variants of adenoid cystic carcinoma presented in standard textbooks in head and neck pathology and in previously published cases

Author [reference]	ADCC-S	ADCC-D		
	Histology	IHC	Histology of dedifferentiated component	IHC
WHO [20]	Sheets of uniform basaloid cells lacking tubular or microcystic formation, although true ducts invariably present	NS	NS	NS
Gnepp [23]	Islands of mainly myoepithelial cells with infrequent true ducts, occasional pseudocysts	NS	NS	NS
Wenig [22]	Little tendency to form ducts, more pleomorphism, increased mitotic activity	NS	Transformation of low grade or ADCC-S to high grade carcinoma	Loss or reduced p63 calponin expression
Cardesa and Slootweg [21]	Small duct like spaces with surrounding epithelial layer	NS	NS	NS
Nagao et al. [25]	NA		Poorly differentiated or undifferentiated carcinoma	No myoepithelial expression (SMA, MSA, GFAP)
Seethela et al. [26]	NA		Poorly differentiated cribriform adenocarcinoma or undifferentiated solid carcinoma	Unclear, possible foci of incomplete staining for myoepithelial markers, S100 protein focal+
Cheuk et al. [27]	NA		Two poorly differentiated adenocarcinomas and one case of sarcomatoid neoplasm with focal myoepithelial features	
Sato et al. [28]	NA		High grade adenocarcinoma	Focal positivity for SMA
Malhotra et al. [29]	NA		Undifferentiated carcinoma	No evidence of myoepithelial differentiation (SMA)
Chao et al. [29]			Poorly differentiated adenocarcinoma	No evidence of myoepithelial differentiation (MSA)

ADCC-S solid variant of adenoid cystic carcinoma, *ADCC-D* dedifferentiated/high-grade transformed adenoid cystic carcinoma, *IHC* immunohistochemistry, *NS* not specified, *NA* not applicable, *SMA* smooth muscle actin, *MSA* muscle specific actin, *GFAP* glial fibrillary acidic protein

transformed components in all cases showed a ductal immunophenotype with strong positivity for keratin, and often with S100 positivity”.

The absence of a definitive myoepithelial differentiation in ADCC-D is supported by the findings of Cheuk et al. who reported on three cases of ADCC-D, two cases were interpreted as poorly differentiated adenocarcinomas and 1 case as a “sarcomatoid neoplasm with focal myoepithelial features” [27], and 1 case of ADCC-D of the maxillary sinus by Sato et al., where the dedifferentiated component was interpreted as a high-grade adenocarcinoma [28]. Furthermore, the high-grade (“dedifferentiated”) components in ADCC-Ds reported by Malhotra et al., Chao et al. and Moles et al. also displayed an absence of myoepithelial differentiation [29–31].

The differential diagnosis between ADCC-S and ADCC-D remains challenging and contentious with different definitions of dedifferentiation from different experts. Perhaps the fusion of *MYB* and *NFIB* transcription factor-genes based on a t(6;9)(q22–23;p23–24) in ADCC of both

salivary gland and breast origin, as shown by Nordkvist et al. [32] and Persson et al. [33] may become a valuable molecular diagnostic tool in better delineating ADCC in the future.

Dedifferentiation in salivary gland carcinomas other than ADCC is a rare but well recognized phenomenon and has been documented in epithelial-myoepithelial carcinoma (EMECa) [34–38], acinic cell carcinoma [39–44], mucoepidermoid carcinoma [45, 46], polymorphous low-grade adenocarcinoma [47, 48], hyalinizing clear cell carcinoma [49] and salivary duct carcinoma [50–53]. In the dedifferentiated (recurrent) acinic cell carcinoma presented by Piana et al. [42], there was evidence of myoepithelial differentiation (clear cell morphology, widespread positivity for S100 protein and focal immunoreactivity for SMA). In none of the other dedifferentiated salivary gland carcinomas referred to above did the dedifferentiated component display diffuse histological or immunohistochemical features of myoepithelial differentiation. In fact, to the best of our knowledge, even in the only reported dedifferentiated myoepithelial carcinoma, by Okawa et al. [54], did the

dedifferentiated component display an undifferentiated carcinomatous phenotype without evidence of myoepithelial differentiation. Moreover, in a paper by Daa et al., the authors present one case of EMECa of the parotid gland harboring a p53 mutation. In this case, the epithelial component formed solid nests which exhibited increased proliferative activity compared to the parts of the tumor which displayed the general biphasic pattern of EMECa. Whether this case represents incipient dedifferentiation or not is not clear to us, but it was the epithelial and not the myoepithelial component that showed evidence of a potentially more “aggressive phenotype”. (That the dedifferentiated component in EMECa appears to display an epithelial phenotype is intriguing when one contemplates the phenomenon of myoepithelial anaplasia (which characteristically is immunohistochemically negative for p53, in contrast to the significant p53-expression in our case)).

Going through the literature, we have found one case published by Toyosawa et al. [55] that occurred in the submandibular gland which showed features similar to our case. The authors labeled the tumor as a “small cell undifferentiated carcinoma with immunohistochemical evidence of myoepithelial, basal and luminal cell features”. This tumor was composed of neoplastic cells “as large as or slightly larger than lymphocytes”, mitoses were numerous and there was presence of necrosis. Only occasional pseudoglandular structures, but not tubules, were seen. The nature of the stroma was not specified. Immunohistochemically, tumor cells were positive for SMA, pan-cytokeratin and vimentin. Neuroendocrine markers were negative, as was S100 protein. Focally there was EMA positivity in a “canalicular manner”. The patient was free of disease 3 years after a radical resection and postoperative radiotherapy (60 Gy). Regarding undifferentiated carcinomas in salivary glands, WHO (2005) recognizes the NPC-type and a large cell variant, neither of which fits the tumor described by Toyosawa et al. or our tumor. Interestingly, the authors highlight previous studies (which seem not to have been appreciated by later investigators, including WHO), describing small cell carcinomas of salivary glands which display ultrastructural evidence of myoepithelial differentiation [56–59].

Based on the absence of true ducts, a distinct and widespread myoepithelial immunophenotype, focal spindling and predominant anaplastic morphology (including a very high proliferation), absence of a low-grade ADCC component and the absence of any significant evidence of a dual cell population, we feel that our case should not be classified as either ADCC-S or ADCC-D, despite the inconsistencies in their definition from the literature. We prefer the term ‘anaplastic myoepithelial carcinoma’ to ‘undifferentiated’ carcinoma since there is clear cut immunohistochemical evidence of extensive myoepithelial differentiation. It is plausible that tumors like our case may

be an under-recognized category of poorly differentiated salivary gland tumors. At a practical level, the absence of traditionally accepted light microscopic features of myoepithelial differentiation in a poorly differentiated salivary gland carcinoma in the sinonasal region, would in many instances trigger the performance of immunohistochemical markers to demonstrate epithelial and neuroendocrine (but not myoepithelial) features, in the absence of which, a diagnosis of an undifferentiated carcinoma, either of salivary gland origin or SNUC, would be rendered.

In summary, we present an unusual high-grade carcinoma of the nasal cavity with distinctive myoepithelial immunophenotype supporting a diagnosis of an anaplastic form of myoepithelial carcinoma. The diagnosis of this rare tumor remains challenging in view of the undifferentiated/anaplastic morphology and lack of awareness. As such, performing a too limited immunohistochemical workup in the diagnosis of malignant poorly differentiated small round cell tumors in the sinonasal tract would result in the under-recognition of such tumors.

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