Newly Described Tumor Entities in Sinonasal Tract Pathology

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Abstract Surgical pathology of the sinonasal tract (nasal cavity and paranasal sinuses) is extremely challenging due in part to the tremendous diversity of tumor types that may arise in this region. Compounding the difficulty, a number of new sinonasal tumor entities have been recently described, and pathologists may not yet be familiar with these neoplasms. This manuscript will review the clinicopathologic features of some of the newly described sinonasal tumor types: NUT midline carcinoma, HPV-related carcinoma with adenoid cystic-like features, SMARCB1 (INI-1) deficient sinonasal carcinoma, biphenotypic sinonasal sarcoma, and renal cell-like adenocarcinoma.

Keywords NUT midline carcinoma · HPV-related carcinoma with adenoid cystic-like features · SMARCB1 (INI-1) deficient sinonasal carcinoma · Biphenotypic sinonasal sarcoma · Renal cell-like adenocarcinoma

Introduction

Despite its relatively small anatomic size, the nasal passages can give rise to a tremendously diverse group of neoplasms ranging from carcinomas to lymphomas and

sarcomas of various types. Indeed, the latest edition of the WHO classification of head and neck tumors includes no fewer than 68 separate tumor entities in the sinonasal tract (nasal cavity and paranasal sinuses) chapter [1]. Nevertheless, in a head and neck surgical pathology consult practice, it is not uncommon to receive a biopsy of a sinonasal neoplasm that does not fit neatly into any of those diagnostic categories. In the 10 years since the last WHO classification was published, considerable strides have been made in sorting some of these difficult-to-characterize tumors into new, distinct tumor entities. Interestingly, most of these newly described diagnostic entities are defined in part on their underlying viral or genetic mechanisms, supporting their separate classification and in some cases, offering potential therapeutic targets for the future. Strong consideration should be given to including these new tumor types into the forthcoming new edition of the WHO classification scheme.

NUT Midline Carcinoma

In 1991, two independent case reports that described mediastinal carcinomas with t(15;19) translocations were published [2, 3]. Since that time, tumors harboring *NUT* translocations have been increasingly recognized, with more than 70 additional reported cases [4–7]. Originally these tumors—known as NUT midline carcinomas (NMCs)—were thought to affect children and young adults primarily, but this is likely due to the fact that pediatric tumors are far more likely to be sent for cytogenetic analysis when compared to tumors arising in adults. With increasing recognition of this entity, it is clear that patients of any age can be affected (0–78 years, median 16) [7]. As its name suggests, NMC generally (though not exclusively)

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Fig. 1 NUT midline carcinoma grows as nests of tumor cells in the sinonasal submucosa (a). NUT midline carcinoma often exhibits a peculiar form of “abrupt” keratinization (b). NUT midline carcinomas have high mitotic rates, but they are very monotonous at the

cellular level, with minimal nuclear pleomorphism (c). The diagnosis is confirmed by NUT-1 immunohistochemistry, which is diffusely positive in a nuclear distribution in NUT midline carcinoma. The immunostaining usually has a speckled quality (d)

affects organs along the midline of the body; the mediastinum and the sinonasal tract are most frequently involved. Unfortunately, in about half of cases, patients present with lymph node and/or distant metastases [7].

NMC is defined by translocations involving *NUT* on chromosome 15q14 [8]. The most frequent partner gene is *BRD4* on chromosome 19, but about one-third of cases have variant rearrangements. This translocation is usually the only genetic alteration found in NMC, and in that regard, is cytogenetically more similar to most lymphomas than carcinomas [5]. These rearrangements may be identified by conventional karyotyping, fluorescence in situ hybridization (FISH), or polymerase chain reaction (PCR)-based methods.

Histologically, NMC is a very poorly differentiated malignancy that grows as nests and sheets of tumor cells. The cell of origin is unknown and an in situ tumor component is almost never seen. NMC is very infiltrative and cytologically high-grade with numerous mitotic figures and frequent tumor necrosis. A clue to its diagnosis is the fact that despite being so clearly high-grade, the tumor nuclei lack the pleomorphism that is typically seen in high-grade carcinomas. In contrast, the nuclei are relatively uniform and monotonous, reflecting its very simple cytogenetic changes as described above. In most NMCs, overt

squamous differentiation is seen in the form of keratinization. The pattern of keratinization is unusual, however, in that it is “abrupt,” i.e., undifferentiated tumor cells are often seen immediately next to highly differentiated keratin pearls that sometimes contain abundant glycogen. This peculiar feature is another clue to the diagnosis of NMC (Fig. 1).

In the sinonasal tract, NMC should be included in the so-called “small round blue cell” differential diagnosis with other malignancies like olfactory neuroblastoma, melanoma, and lymphoma (see [9]). Retrospective studies have shown that NMCs were previously most likely to be diagnosed as sinonasal undifferentiated carcinoma (SNUC) or poorly differentiated squamous cell carcinoma [10, 11]. Immunohistochemistry is very helpful in the differential diagnosis, as NMC is always positive for cytokeratin, usually positive for p63 and p40 [12], and almost always negative for neuroendocrine markers like synaptophysin and chromogranin. CD34 is positive in about half of NMCs, which can be helpful since carcinomas are only rarely positive for this marker [6]. NMC is always negative for the oncoviruses human papillomavirus (HPV) and Epstein-Barr virus (EBV).

Ultimately, the diagnosis of NMC requires documenting the presence of a *NUT* rearrangement. While this may be

done by molecular analysis, recently an immunohistochemical stain for NUT-1 protein (Cell Signaling Technologies, Danvers, MA) has been introduced and found to be highly sensitive and specific for the diagnosis of NMC [13]. In fact, diffuse (>50 %) positivity for NUT-1 is now considered sufficient evidence for NUT rearrangement, meaning that the diagnosis may be made without the need for highly specialized genetic testing [4, 5, 13]. NUT-1 immunostaining is nuclear in distribution and has a characteristic granular or speckled quality (Fig. 1).

The importance of correctly diagnosing NMC is both prognostic and therapeutic [5]. While complete resection with adjuvant radiotherapy improves prognosis, NMC is highly aggressive and its prognosis is currently dismal, with a mean survival of only 6.7 months [7]. Conventional chemotherapeutic agents are ineffective [7]. Fortunately, though, the presence of a translocation has opened the door to novel, targeted biologic agents including bromodomain inhibitors and histone deacetylase inhibitors [4, 5]. Trials investigating these drugs are underway. Making a correct diagnosis of NMC allows the affected patient to be enrolled into the international NUT midline carcinoma registry (www.nmcregistry.org) which follows patients' outcomes and may direct them to the institutions running these trials [4, 5].

Considering then the implications of correctly diagnosing NMC, it is reasonable to wonder whether every sinonasal carcinoma should be tested for *NUT* rearrangement, at least by immunohistochemistry. Fortunately, the answer appears to be no. Even though NMC is still very likely underdiagnosed, retrospective studies have shown that it is still a rare neoplasm [4, 10, 14, 15]. At Johns Hopkins, we tested 151 consecutive sinonasal carcinomas of all histologic types by NUT-1 immunohistochemistry, and only three cases were positive [10]. Moreover, all three conformed to the histology expected for NMC. Accordingly, it appears that among sinonasal carcinomas, only those with an undifferentiated component and without overt glandular differentiation should be tested for *NUT* rearrangement. Those with well-developed glandular differentiation or that are virally-driven (HPV or EBV) can be safely excluded.

HPV-Related Carcinoma with Adenoid Cystic-Like Features

It is well recognized that the rate of head and neck squamous cell carcinomas caused by HPV is on the rise, and numerous studies have definitively established the oropharynx (palatine tonsils and base of tongue) as the anatomic site where most HPV-related squamous cell carcinomas originate [16, 17]. Using accurate methods to detect transcriptionally active HPV, up to 80 % of

oropharyngeal carcinomas are caused by the virus, compared to <5 % in sites like the oral cavity and larynx [18–22]. However, several recent papers have shown that the sinonasal tract is the second anatomic “hot spot” from which HPV-related carcinomas can arise. Indeed, it appears that approximately 20–25 % of carcinomas arising from the sinonasal tract harbor high-risk types of HPV [23–25]. Most HPV-related sinonasal carcinomas have a histologic appearance similar to their oropharyngeal counterparts: a basaloid-appearing squamous cell carcinoma with minimal keratinization. However, a subset of HPV-related sinonasal carcinomas closely resembled salivary gland tumors, especially adenoid cystic carcinomas. We have referred to these carcinomas as HPV-related carcinomas with adenoid cystic-like features [26].

Our original series of HPV-related carcinomas with adenoid cystic-like features included eight cases. Since its publication we have encountered seven additional cases (unpublished data), and one case report from another institution has been published [27]. The patients have consisted of ten women and six men ranging in age from 35 to 73 years (mean 53), and they present with obstruction and/or epistaxis.

As the name suggests, sinonasal HPV-related carcinomas with adenoid cystic-like features have considerable morphologic overlap with salivary adenoid cystic carcinoma, particularly its solid variant. They grow as nests, sheets, or trabeculae of basaloid cells that are predominantly solid; most cases, however, do exhibit at least a focal cribriform growth pattern with microcystic spaces containing basophilic material. The tumors typically feature abundant mitotic activity and may contain cellular necrosis, although they are not usually very infiltrative. By immunohistochemistry, the similarities with adenoid cystic carcinoma persist. Sinonasal HPV-related carcinomas with adenoid cystic-like features have two cell types: the basaloid myoepithelial cells which are positive for one or more myoepithelial markers (e.g., calponin, p63, p40, actin, S100) and the ductal cells which are positive for c-kit (Fig. 2).

Despite many similarities with adenoid cystic carcinoma, HPV-related carcinoma with adenoid cystic-like features is also distinct in many important ways. First, unlike adenoid cystic carcinoma which can arise virtually anywhere in the head and neck, HPV-related carcinoma with adenoid cystic-like features has so far only been encountered in the sinonasal tract. Second, most cases have areas of overlying squamous dysplasia, strongly suggesting that the tumor is arising from the surface epithelium, and not the seromucinous glands. Third, the tumor cells and the overlying dysplastic epithelium are both positive for p16 and high-risk HPV by in situ hybridization (usually the rare type 33). Most evidence shows that true salivary tumors are

Fig. 2 HPV-related carcinoma with adenoid cystic-like features grows as basaloid nests, trabeculae, and cribriform structures. The surface exhibits squamous dysplasia. **a** Like adenoid cystic carcinoma, HPV-related carcinoma with adenoid cystic-like features is

biphasic with myoepithelial cells that are positive for p63 (**b**) and ducts that are positive for c-kit (**c**). Both the invasive tumor and the dysplastic surface are positive for p16 by immunohistochemistry (**d**) and HPV by in situ hybridization (*inset*)

not caused by this virus [24, 26, 28]. Finally, sinonasal HPV-related carcinomas with adenoid cystic-like features lack translocations for *MYB*, the genetic alteration that is specific for adenoid cystic carcinoma and is seen in more than half of cases [29, 30].

The differential diagnosis of sinonasal HPV-related carcinoma with adenoid cystic-like features includes other HPV-related variants like basaloid squamous cell carcinoma and adenosquamous carcinoma. The presence of true ducts and the absence of squamous differentiation in the invasive tumor help to rule out basaloid squamous cell carcinoma, and the myoepithelial differentiation of the basaloid tumor cells excludes adenosquamous carcinoma. Even though the tumor name highlights similarities to adenoid cystic carcinoma, sinonasal HPV-related carcinoma with adenoid cystic-like features may also resemble other salivary tumor types like epithelial-myoepithelial carcinoma and basal cell adenocarcinoma. In fact, the diagnosis of HPV-related carcinoma with adenoid cystic-like features should be considered for any sinonasal tumor that has a salivary-like appearance but does not neatly fit into any specific tumor category. The presence of clear-cut squamous dysplasia and the presence of high-risk HPV confirm the diagnosis. It should be remembered that p16 immunohistochemistry alone should not be used as a

surrogate for HPV outside of the oropharynx. Indeed, salivary gland cancers including adenoid cystic carcinoma may be positive for p16 [26, 31].

The prognostic significance of HPV-related carcinoma with adenoid-cystic like features is not yet clear given the relative rarity of these cases. It is worth noting, however, that despite its morphologic similarity to high-grade adenoid cystic carcinoma, in limited experience only two tumors have locally recurred and none have metastasized [26, 27].

SMARCB1 (INI-1) Deficient Sinonasal Carcinoma

SMARCB1 (*INI-1*) is a tumor suppressor gene located on chromosome 22q11.2, and its gene product is ubiquitously expressed in nuclei of all normal tissues. *SMARCB1* inactivation has been implicated in the pathogenesis of a diverse group of malignant neoplasms that share “rhabdoid” morphologic features. This group of SMARCB1 (INI-1) deficient tumors includes atypical teratoid/rhabdoid tumor of the central nervous system, malignant rhabdoid tumors of the kidney and soft tissue [32–38], epithelioid sarcoma [39–41], renal medullary carcinoma [42], myoepithelial carcinoma of soft tissue [39, 43], epithelioid

malignant peripheral nerve sheath tumor [39], and extraskeletal myxoid chondrosarcoma [44]. Recently, our group and Agaimy et al. independently introduced a new member of the SMARCB1 (INI-1) deficient tumor family: SMARCB1 (INI-1) deficient sinonasal carcinoma [45, 46].

Twelve SMARCB1 (INI-1) deficient sinonasal carcinomas have been described, arising in five men and seven women ranging in age from 28 to 78 (mean 54). They presented with symptoms like pain, eye symptoms, and obstruction. These carcinomas tend to grow as epithelioid nests in the sinonasal submucosa. Tumor necrosis is usually seen, and the mitotic rate is typically high. These tumors are usually highly infiltrative, with frequent bone invasion. At the cellular level, each SMARCB1 (INI-1) deficient sinonasal carcinoma contained some cells that are recognizable as rhabdoid or plasmacytoid, but the number of these cells is variable. In some cases they predominate and are very noticeable, while in other examples they are singly dispersed among more basaloid tumor cells. While the tumor cell cytoplasm is variable in quality, the tumor nuclei of these carcinomas tend to be uniformly round with open chromatin and a prominent nucleolus (Fig. 3). Nuclear pleomorphism is not typical. None of the SMARCB1 (INI-1) deficient sinonasal carcinomas has shown overt squamous or glandular differentiation, and an in situ carcinoma component is not seen.

The consistent immunophenotypic features of SMARCB1 (INI-1) deficient carcinoma are strong, diffuse cytokeratin expression along with a complete absence of SMARCB1 (INI-1) immunostaining (Fig. 3). Five of 11 cases were focally positive for synaptophysin, 4 of 9 were positive for p63 and p40 (with diffuse expression in 3 of 4 positive cases), and 1 of 12 cases showed focal S100 immunostaining. All cases were negative for actin, desmin, chromogranin, and NUT-1. Interestingly, 3 of 12 cases showed diffuse positivity for p16, but all 12 cases were negative for high risk HPV by in situ hybridization or PCR. In the eight cases where *SMARCB1 (INI-1)* FISH was successfully performed, six showed copy number alterations: homozygous deletion of *SMARCB1* in five cases and a heterozygous deletion pattern in one. The lack of *SMARCB1* deletions in two cases raises the possibility of alternative inactivating events below the FISH resolution (e.g., intragenic mutations, small deletions or epigenetic silencing).

SMARCB1 (INI-1) deficient sinonasal carcinoma may be confused for a non-keratinizing or basaloid form of squamous cell carcinoma. If diffuse p63 or p40 immunolabeling is seen, this can cause further confusion for squamous cell carcinoma, and diffuse p16 staining may also suggest that the tumor is HPV-related. However,

Fig. 3 SMARCB1 (INI-1) deficient sinonasal carcinoma invades as basaloid nests beneath a normal surface epithelium. Tumor necrosis is evident (a). SMARCB1 (INI-1) deficient sinonasal carcinoma is typically highly infiltrative, with frequent invasion of bone (b).

Variable numbers of rhabdoid tumor cells are frequently found in SMARCB1 (INI-1) deficient sinonasal carcinoma (c). By definition, this entity is completely negative for SMARCB1 (INI-1) by immunohistochemistry (d)

SMARCB1 (INI-1) deficient sinonasal carcinoma does not show squamous differentiation or surface squamous dysplasia, and more specific HPV testing is consistently negative. Another diagnostic consideration is SNUC. However, the tumor cells of SNUC are typically more pleomorphic than what is encountered in SMARCB1 (INI-1) deficient sinonasal carcinomas [47]. Moreover, SNUC is generally regarded as a diagnosis of exclusion, and is not used when a more specific diagnosis can be given (e.g., cases now recognized as NUT midline carcinoma, as described above). When confronted with a basaloid carcinoma in the sinonasal tract without clear-cut squamous or glandular differentiation, a search for rhabdoid cells and a low threshold for SMARCB1 (INI-1) immunostaining are warranted. Finally, epithelioid sarcoma may be considered in the differential diagnosis on the basis of cytokeratin expression, SMARCB1 (INI-1) deficiency and *SMARCB1* (*INI-1*) gene alterations. However, SMARCB1 (INI-1) deficient sinonasal carcinoma generally has a distinctly nested and basaloid growth pattern similar to other forms of sinonasal carcinoma, and lacks the sheet-like, pseudo-granulomatous growth of dyscohesive cells characteristic of epithelioid sarcoma. CD34 immunostaining may be helpful in this differential, as about half of epithelioid sarcomas are positive for this antibody.

While the number of reported cases is limited, SMARCB1 (INI-1) deficient sinonasal carcinoma appears to be an aggressive tumor, with frequent local invasion into the brain and/or skull base. Six of 9 cases with known staging information presented at T4 [46]. Patients have generally been treated with a combination of surgery, chemotherapy, and radiation, and so far, 4 of 11 patients experienced local recurrence, 5 of 11 had regional or distant metastasis, and 5 of 11 patients have died of their disease [46, 48].

Biphenotypic Sinonasal Sarcoma

Lewis et al. [49] recently described a group of low-grade spindle cell sarcomas arising exclusively in the sinonasal tract and named them “low-grade sinonasal sarcoma with neural and myogenic differentiation.” The same group subsequently renamed the entity biphenotypic sinonasal sarcoma (BSNS) [50]. Thirty-six cases of BSNS have been reported [49–52]. They typically arise in the superior aspects of the nasal cavity and ethmoid sinuses of women (M:F ratio is 1:3) ranging in age from 24 to 85 (mean 52). Patients have presented with non-specific symptoms like nasal congestion and facial pressure.

Histologically, BSNS is a poorly circumscribed and unencapsulated, uniformly hypercellular proliferation of intersecting fascicles. A “herringbone” fascicular pattern is

commonly seen, and “staghorn” vessels are also common. The tumor cell nuclei are elongated, uniform, and hypochromatic. A feature that is diagnostically quite useful is the frequent presence of hyperplastic respiratory surface epithelium extending downward and entrapped by the spindle cell tumor (Fig. 4). BSNS is histologically low-grade, lacking high mitotic rates and necrosis. By immunohistochemistry, BSNS characteristically expresses smooth muscle actin, calponin, and S100. BSNS is sometimes also focally positive for desmin, EMA, and cytokeratins (Fig. 4). Almost all examples of BSNS harbor rearrangements of *PAX3*, and the most frequent translocation partner is *MAML3*. *PAX3-MAML3* appears to be specific for BSNS [50]. Huang et al. [51] recently described a subset of BSNS cases with the same *PAX3-NCOA1* fusions that can be seen in alveolar rhabdomyosarcoma. Interestingly, these *PAX3-NCOA1* tumors often harbor focal rhabdomyoblastic differentiation, with rare strap cells and myogenin immunoreactivity.

BSNS has only recently been recognized as a distinct entity, and it was likely misdiagnosed as several different neoplasms in the past. Its S100 positivity may suggest a nerve sheath tumor like schwannoma or malignant peripheral nerve sheath tumor. Certainly schwannomas of the sinonasal tract are unencapsulated and can be very hypercellular [53]. However, while BSNS is S100 positive, it is generally not as diffusely immunoreactive as schwannoma, where essentially every cell is strongly positive. In addition, the presence of smooth muscle differentiation argues against schwannoma, and unlike schwannoma, BSNS has been consistently negative for SOX-10 [51]. Malignant peripheral nerve sheath tumor may, like BSNS, show aberrant muscle (i.e., malignant triton tumor) or epithelial differentiation. However, malignant peripheral nerve sheath tumor is generally much higher grade than BSNS, with necrosis and considerable nuclear pleomorphism. It is likely that examples in the literature diagnosed as “low-grade” malignant triton tumor are, in fact, BSNS [54]. Given the focal cytokeratin immunostaining and uniform nuclear features, a monophasic synovial sarcoma is another diagnostic consideration. However, all cases of BSNS have been negative for synovial sarcoma fusion transcripts [49, 50]. Finally, the staghorn vasculature raises the possibility of glomangiopericytoma or solitary fibrous tumor. The spindled cells and S100 positivity of BSNS argues against glomangiopericytoma which is more epithelioid and S100 negative. In addition, BSNS lacks the characteristic ropey collagen and variable cellularity of solitary fibrous tumor, which is also S100 negative. Finally, the presence of the *PAX3* rearrangement characteristic of BSNS is not found in any of the other diagnostic considerations.

Clinically, BSNS behaves relatively indolently. Almost half of patients with BSNS have experienced local

Fig. 4 Biphenotypic sinonasal sarcoma is a highly cellular spindle cell proliferation. Frequently, non-neoplastic surface glands become entrapped within the tumor (a). The tumor cells of biphenotypic sinonasal sarcoma are arranged in fascicles, sometimes in an

alternating “herringbone” pattern (b). Biphenotypic sinonasal sarcoma is almost always focally positive for both actin (c) and S100 protein (d)

Fig. 5 Sinonasal renal cell-like adenocarcinoma grows as nests and follicles (a) of cells with abundant, optically clear cytoplasm (b). Unlike true renal cell carcinoma, however, sinonasal renal cell-like

adenocarcinoma is often positive for S100 (c) and is always negative for the renal-specific marker PAX-8 (d)

recurrences, but none of the tumors have metastasized, and none of the patients have died of their disease [49, 50].

Renal Cell-Like Adenocarcinoma

Initially reported in 2002, a total of 13 cases of a tumor known as sinonasal renal cell-like adenocarcinoma have been reported [55–58]. This tumor has presented in nine women and four men ranging in age from 22 to 77 (mean 54) that presented with epistaxis [55–58]. The tumor is defined by its histologic similarity to clear cell renal cell carcinoma. Sinonasal renal cell-like adenocarcinoma consists of nests and follicles of polyhedral cells with abundant optically clear cytoplasm. Some cases even contain prominent intrafollicular hemorrhage, a classic feature of clear cell renal cell carcinoma. Nuclear pleomorphism and mitotic activity are minimal (Fig. 5). Sinonasal renal cell-like adenocarcinoma is consistently positive for CK7, sometimes positive for S100, and negative for high-molecular weight cytokeratins, actin, and calponin [55, 56].

The main diagnostic dilemma is distinguishing sinonasal renal cell-like adenocarcinoma from metastatic renal cell carcinoma, which metastasizes to the head and neck not infrequently. In contrast to clear cell renal cell carcinoma, sinonasal renal cell-like adenocarcinoma is consistently negative for the immunohistochemical markers PAX8, RCC, and vimentin. Other diagnostic considerations include the minor salivary gland tumors hyalinizing clear cell carcinoma, mucoepidermoid carcinoma, and myoepithelial carcinoma. Sinonasal renal cell-like adenocarcinoma lacks squamoid or mucinous cells, helping eliminate hyalinizing clear cell carcinoma and mucoepidermoid carcinoma from consideration. In addition, both of those salivary-type tumors have characteristic translocations involving *EWSR1* and *MAML2*, respectively [59, 60]. The absence of calponin, actin, and high-molecular weight cytokeratins helps to exclude a myoepithelial neoplasm.

Sinonasal renal cell-like adenocarcinoma appears to be a very indolent neoplasm. None of the four patients with sinonasal renal cell-like adenocarcinoma have experienced recurrence or metastatic disease [55, 56].

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