

New tumor entities in the 4th edition of the World Health Organization classification of head and neck tumors: Nasal cavity, paranasal sinuses and skull base

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Abstract The World Health Organization recently published the 4th edition of the Classification of Head and Neck Tumors, including several new entities, emerging entities, and significant updates to the classification and characterization of tumor and tumor-like lesions, specifically as it relates to nasal cavity, paranasal sinuses, and skull base in this overview. Of note, three new entities (NUT carcinoma, seromucinous hamartoma, biphenotypic sinonasal sarcoma,) were added to this section, while emerging entities (*SMARCB1*-deficient carcinoma and HPV-related carcinoma with adenoid cystic-like features) and several tumor-like entities (respiratory epithelial adenomatoid hamartoma, chondromesenchymal hamartoma) were included as provisional diagnoses or discussed in the setting of the differential diagnosis. The sinonasal tract houses a significant diversity of entities, but interestingly, the total number of entities has been significantly reduced by excluding tumor types if they did not occur exclusively or predominantly at this site or if they are discussed in detail elsewhere in the book. Refinements to nomenclature and criteria were provided to sinonasal papilloma, borderline soft tissue tumors, and neuroendocrine neoplasms. Overall, the new WHO classification reflects the state of current understanding for many relatively rare neoplasms, with this article highlighting the most significant changes.

Keywords Nasal cavity · Paranasal sinuses · Skull base · Tumor · WHO · Carcinoma, squamous cell · *SMARCB1*-deficient carcinoma · HPV-related adenoid cystic carcinoma · Sinonasal papilloma · Biphenotypic sinonasal sarcoma · Neuroectodermal tumors · Adenocarcinoma, sinonasal type · Immunohistochemistry

Introduction

The 2017 4th edition of the World Health Organization classification of tumors of the head and neck, specifically as it relates to the nasal cavity, paranasal sinuses, and skull base (chapter 1, herein after referred to collectively as sinonasal tract), has undergone a complete overhaul [1]. The sinonasal tract encompasses a wide diversity of entities, but significantly, the number of entities has been reduced by omitting tumors or tumor-like lesions when they do not occur exclusively or predominantly at this site or if they are discussed in detail elsewhere in the book. The chapter is separated into major groups, from the most common malignant epithelial tumors (squamous cell carcinoma) [2, 3], followed by the newly included NUT carcinoma [4], then neuroendocrine carcinoma [5], adenocarcinoma [6, 7], and teratocarcinosarcoma [8], before benign epithelial proliferations (papilloma [9–11], respiratory epithelial lesions [12, 13] and salivary gland tumors) are discussed. Malignant, borderline, and benign soft tissue tumors include the newly described biphenotypic sinonasal sarcoma [14] and a more complete description of epithelioid hemangioendothelioma and chondromesenchymal hamartoma [15]. Brief descriptions of extranodal NK/T cell lymphoma and extrasosseous plasmacytoma highlight only the findings within the sinonasal tract. Finally, the neuroectodermal and melanocytic tumors are included, specifically addressing only the significant findings in the sinonasal tract. The classification reflects the current state of understanding for these uncommon entities, and this article will

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cover entities in the same order as the book, specifically focusing on changes, nomenclature revisions, and new or provisional entities.

Squamous cell carcinoma: keratinizing and non-keratinizing

Squamous cell carcinoma is by far the most common malignancy of the sinonasal tract. The keratinizing (KSCC), non-keratinizing (NKSCC), spindle cell (sarcomatoid), and lymphoepithelial variants are recognized [2, 3]. Other variants, including the verrucous, papillary, basaloid, adenosquamous, and acantholytic, are rare at this anatomic site and have not been included in this new edition in the sinonasal chapter, as they are completely described in sections devoted to other sites where they are more commonly encountered.

KSCC is histologically identical to those tumors arising elsewhere in the upper aerodigestive tract, with nests and cords of tumor cells with variable degrees of keratinization, eliciting a desmoplastic stromal reaction. NKSCC accounts for 15 to 25% of sinonasal SCC. It has a distinctive growth pattern, with invaginating interconnecting ribbons of squamous epithelium with minimal or no evidence of keratinization, and sharply demarcated epithelial-stromal interface, usually with no accompanying desmoplasia. There is maturation of tumor cells with peripheral columnar cells that often show palisading and superficial cells that tend to become flattened. High mitotic activity and areas of necrosis are commonly seen [2].

Sinonasal KSCC and NKSCC show relevant differences in their clinico-pathologic and molecular features, and therefore their separation is relevant. Transcriptionally active high-risk HPV is more frequently detected in NKSCC than in KSCC (35–50 and 0–15%, respectively), although the clinical significance of HPV positivity in sinonasal SCC has not been conclusively assessed as for the oropharynx, and more data need to be collected [16–21]. Moreover, similarly to the oropharynx, absence of *TP53* mutation and intact *CDKN2A/B* are significantly associated with HPV-positive status in sinonasal carcinoma [22].

The recently described sinonasal HPV-related carcinoma with adenoid cystic-like features is discussed within the chapter on NKSCC [23]. As the name implies, the histology of this tumor resembles quite closely that of adenoid cystic carcinoma, being formed by solid and cribriform structures of relatively uniform basaloid cells (Fig. 1). Small duct-like structures can be identified in the solid areas, but squamous differentiation is absent. Immunohistochemically, a dual population of myoepithelial cells positive for calponin, p63, actin, and S100, surround a population of c-kit-positive ductal cells. p16 is diffusely positive. The overlying squamous epithelium

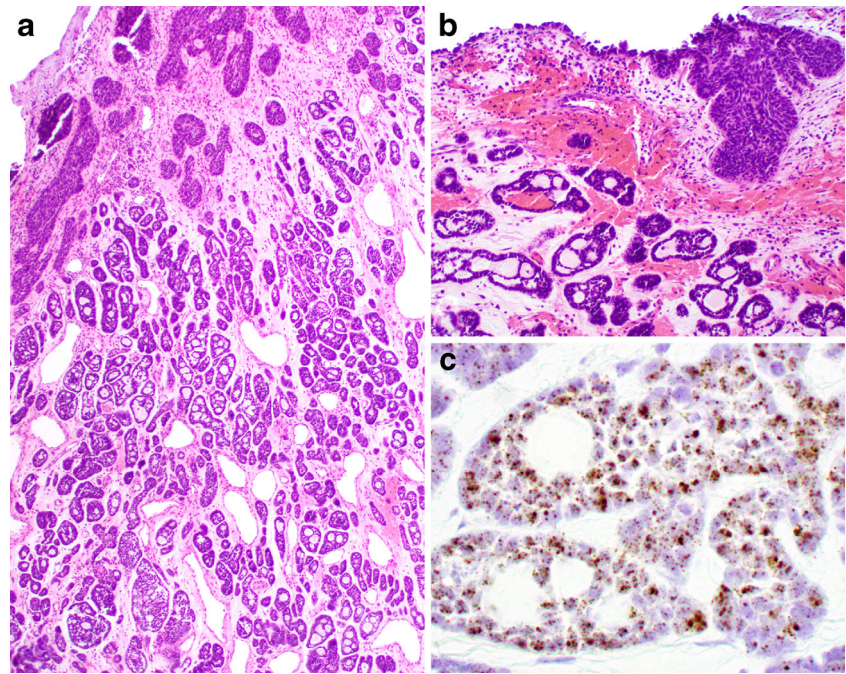
shows signs of dysplasia/carcinoma in situ (Fig. 1), suggesting that the tumor originates from the surface epithelium, rather than from glands, which is a reason to keep it separate from adenoid cystic carcinoma. Other relevant differences with adenoid cystic carcinoma are the absence of *MYB* gene rearrangements and the presence of high-risk HPV (Fig. 1), usually the rare type 33. In the few cases reported so far, the clinical behavior seems to be less aggressive than other high-grade sinonasal malignancies [23, 24]. However, more cases need to be studied to confirm these data and before this tumor can be fully recognized as a separate entity.

Both NKSCC and KSCC may arise from sinonasal papillomas. Recently, molecular evidence in support of a role of precursor lesions for sinonasal papillomas has been provided with the identification of the same activating somatic *EGRF* mutations in the carcinoma and the inverted papilloma [25], and of *KRAS* mutations in oncocytic papilloma and associated carcinoma [26].

NUT carcinoma

NUT carcinoma is a recently characterized entity that is listed in the WHO classification of sinonasal tumors for the first time [4]. It is defined as a poorly differentiated carcinoma, often with evidence of squamous differentiation, which presents a rearrangement of the nuclear protein in testis (*NUTM1*) gene on chromosome 15q14. In most cases, the partner gene of the fusion is *BRD4* (bromodomain-containing protein 4) on 19p13.1, and less frequently *BRD3* or *WHSC1L1*. Other anatomic sites of the head and neck may be involved but most cases arise in the nasal cavity and paranasal sinuses [27]. It affects patients of all ages with a predilection for young adults. Histologically, it is a high-grade poorly differentiated carcinoma with “round blue cell” morphology (Fig. 2). Foci of mature keratinized squamous cells may be occasionally seen abruptly juxtaposed to the undifferentiated component (Fig. 2). Brisk mitotic activity, apoptotic bodies, and areas of necrosis are often recognized. The diagnosis requires the identification of *NUTM1* gene rearrangement, by FISH or RT-PCR. However, diffuse (>50%) immunohistochemical nuclear staining for NUT (Fig. 2) is considered sensitive and specific enough to support the diagnosis of NUT carcinoma [28]. In addition, NUT carcinoma is positive for cytokeratins, p63, and CD34 (in approximately half of the cases), while it is negative for S100, HMB45, desmin, myoglobin, smooth muscle actin, muscle actin, chromogranin, synaptophysin, CD45, placental alkaline phosphatase, alpha-fetoprotein, neuron specific enolase, CD57, and CD99. HPV and EBV have been negative in all cases tested. NUT carcinoma is a highly aggressive tumor with a median survival <1 year. However,

Fig. 1 HPV-related carcinoma with adenoid cystic-like features. The tumor consists of solid and cribriform nests of basaloid cells invading the sinonasal mucosa (a). High-grade squamous dysplasia is present in the overlying surface epithelium (b). RNA in situ hybridization for high-risk HPV is diffusely positive (c) (case courtesy Dr. J. A. Bishop)



the recent evidence of clinical response to targeted treatments with bromodomain inhibitors underscores the importance of its distinction from other poorly differentiated carcinomas of the sinonasal tract [29].

Sinonasal undifferentiated carcinoma

This entity is retained from the previous edition, and it is defined as an undifferentiated carcinoma without glandular

or squamous features and not otherwise classifiable [30]. Thus, it mainly remains a diagnosis of exclusion, requiring separation from several other epithelial and non-epithelial high-grade sinonasal malignancies. The recently described subset of undifferentiated carcinomas with rhabdoid histologic features and loss of *SMARCB1* (INI1) is retained under the umbrella of sinonasal undifferentiated carcinoma (SNUC) as it is still not clear whether it represents a distinct entity. These are highly aggressive carcinomas histologically composed of infiltrating nests of relatively uniform basaloid cells (Fig. 3)

Fig. 2 NUT carcinoma appears as an undifferentiated carcinoma composed of solid sheets of round cells (a). Foci of abrupt keratinization can be appreciated within nests of basaloid cells (arrow) (b). Nuclear positivity for NUT with a distinctive speckled pattern confirms the diagnosis (c)

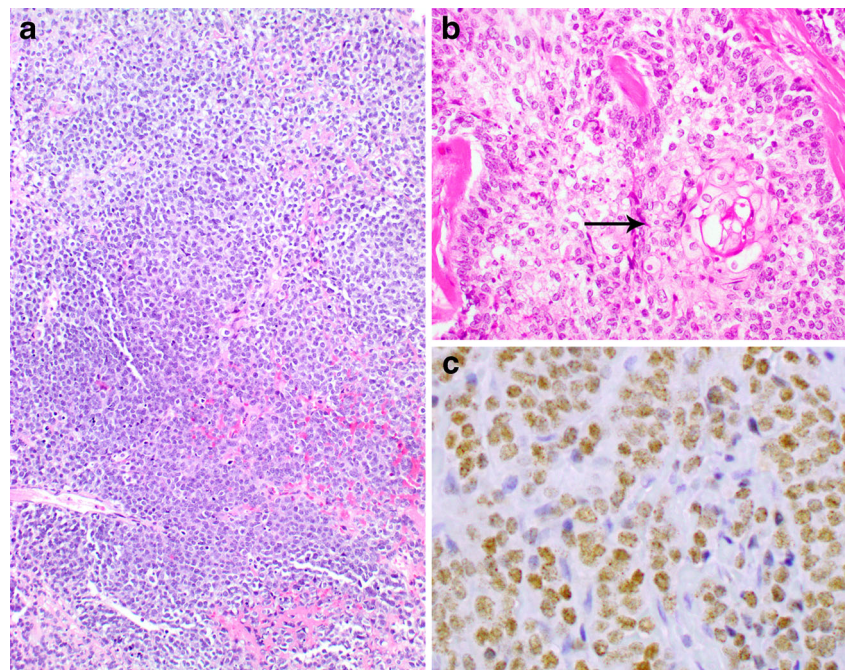
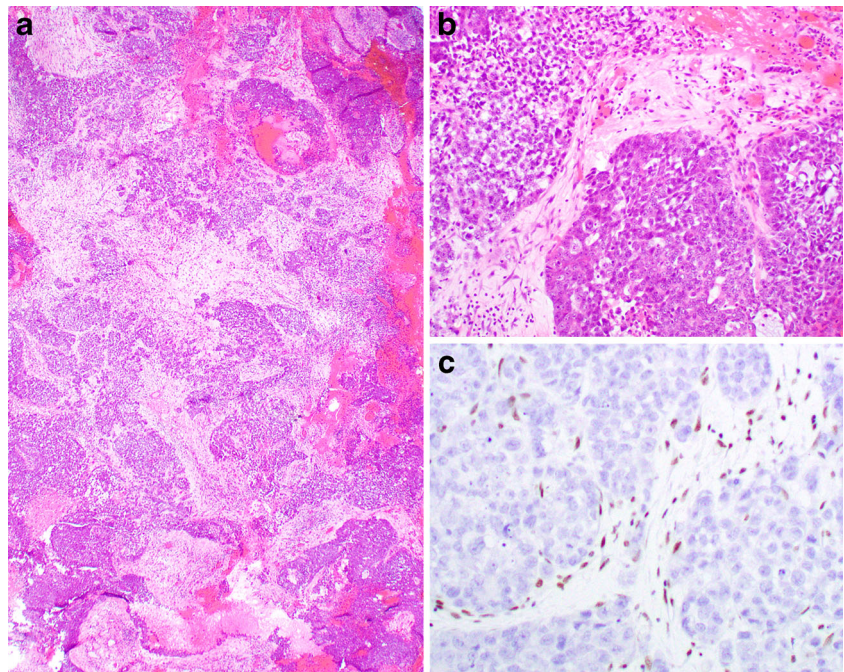


Fig. 3 Sinonasal *SMARCB1*-deficient carcinoma consists of infiltrating nests of undifferentiated basaloid cells (a). Some elements are larger and present a rhabdoid morphology (b). Loss of *SMARCB1* (INI1) expression by neoplastic cells is necessary for the diagnosis. The staining is retained by stromal cells (c)



but at least some elements have abundant, eccentric, eosinophilic cytoplasm, imparting a rhabdoid appearance [31–33]. The hallmark of these tumors is the complete loss of *SMARCB1* expression by immunohistochemistry (Fig. 3), which is associated in most cases with homozygous deletion of *SMARCB1* [31].

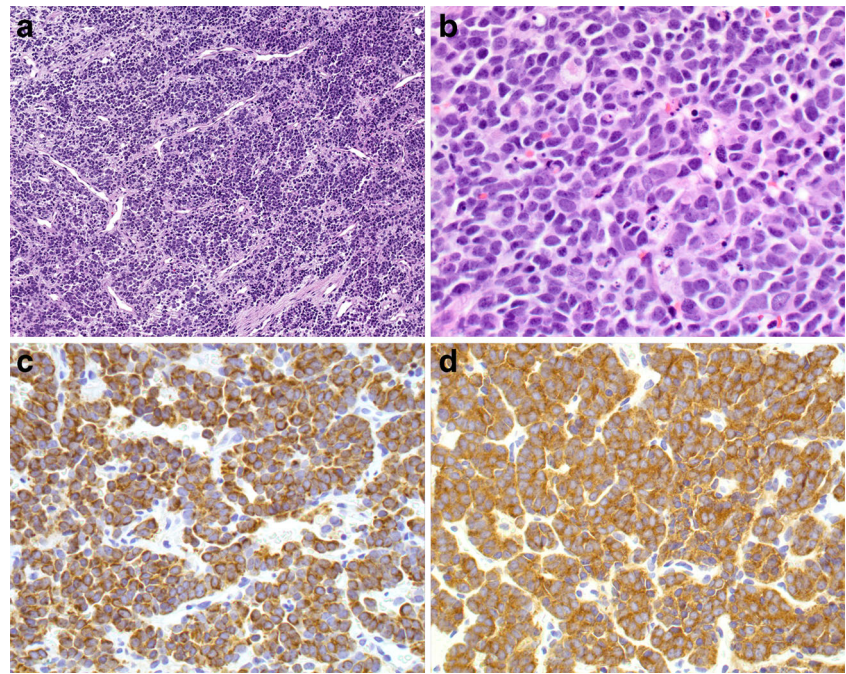
Using next-generation sequencing, *IDH2* mutations at R172 were recently identified in 6 of 11 (55%) SNUCs [34]. This suggests the existence of other genomically defined subsets of undifferentiated carcinomas within the spectrum of SNUC.

Neuroendocrine carcinoma: small cell and large cell types

Originally, SNT neuroendocrine neoplasms were not going to be separated out as a specific chapter, but consensus discussion felt the differential consideration and overlap with other SNT entities demanded inclusion. The previous edition referred to these as neuroendocrine tumors and used the terms typical carcinoid, atypical carcinoid, and small cell carcinoma, neuroendocrine type. Typical carcinoid is so vanishingly rare in this site; it was not specifically addressed. But, in keeping with other anatomic sites, neuroendocrine carcinoma is the preferred nomenclature, separated into small cell and large cell types. Sinonasal neuroendocrine carcinoma (SNEC) is a high-grade malignant epithelial neoplasm showing morphologic (i.e., light microscopic) as well as immunohistochemical features of neuroendocrine differentiation [5]. The specific histologic features of small cell and large cell neuroendocrine carcinomas are morphologically identical to the much more common lung counterparts and thus do not need

to be presented in detail here. However, many sinonasal malignancies show neuroendocrine features, such as olfactory neuroblastoma (ONB), SNEC, NUT carcinoma, and SNUC, while ectopic pituitary adenoma and paraganglioma are benign tumors within the neuroendocrine category. Thus, accurate separation is necessary due to differences in management and therapies employed. In short, SNEC are rare (~3% of sinonasal tract tumors), usually seen in middle- to older-aged patients, and primarily in men [35–38]. Rare cases show an association with transcriptionally active high-risk HPV [19, 20], but curiously there is not the same strong smoking association seen in other organs [39]. Patients present at an advanced stage with frequently local and distant metastases, especially in small cell carcinoma [38, 40, 41]. Importantly, the neoplastic cells must show light microscopic evidence of neuroendocrine differentiation, even though epithelial features tend to be more easily identified in SNT neoplasms. The tumors show significant destructive infiltration of the bones of the midface. Prominent crush artifacts and tumor necrosis along with a high mitotic index may hinder interpretation. Significantly, there is a lack of neurofibrillary stroma, no glandular or squamous differentiation, and generally a minimal to absent lymphoid infiltrate (Fig. 4) [42, 43]. SCC or adenocarcinoma that lack light microscopic features of neuroendocrine differentiation even when showing focal or patchy neuroendocrine immunoreactivity must still be kept in the original category, not diagnosed as neuroendocrine carcinomas. The dot-like or paranuclear reactivity with keratins (Fig. 4) or other neuroendocrine markers is a feature usually seen in neuroendocrine tumors rather than other neoplasms in the differential diagnosis [42, 44–46]. Ultimately, these are biologically aggressive tumors which require multimodality therapy [35, 40, 47, 48].

Fig. 4 Sinonasal small cell neuroendocrine carcinoma consists of nests of uniform round cells infiltrating the mucosa (a). In large cell neuroendocrine carcinoma, the nuclei are more irregular and some contain prominent nucleoli (b). Tumor cells are positive for pancytokeratin (paranuclear dot) (c) and for synaptophysin (d)



Adenocarcinoma: intestinal-type and non-intestinal-type

As in the previous edition, sinonasal adenocarcinomas are further distinguished as intestinal type and non-intestinal type [6, 7]. The intestinal-type adenocarcinoma (ITAC) is morphologically and immunophenotypically similar to primary adenocarcinomas of the intestines (Fig. 5).

Neoplastic cells are typically positive for markers of intestinal differentiation, including cytokeratin 20, CDX2 (Fig. 5), MUC2, and villin. Their separation from other glandular-type sinonasal neoplasms is important because of the strong relationship with occupational exposures to wood and leather dusts and for the frequent aggressive behavior. They have a papillary, tubular, solid, or mixed growth pattern, and a minority of cases shows abundant

Fig. 5 Well-differentiated sinonasal intestinal-type adenocarcinoma (a), with diffuse immunopositivity for CDX2 (b). Low-grade non-intestinal-type adenocarcinoma with predominantly tubular pattern (c) and absent CDX2 expression (d)

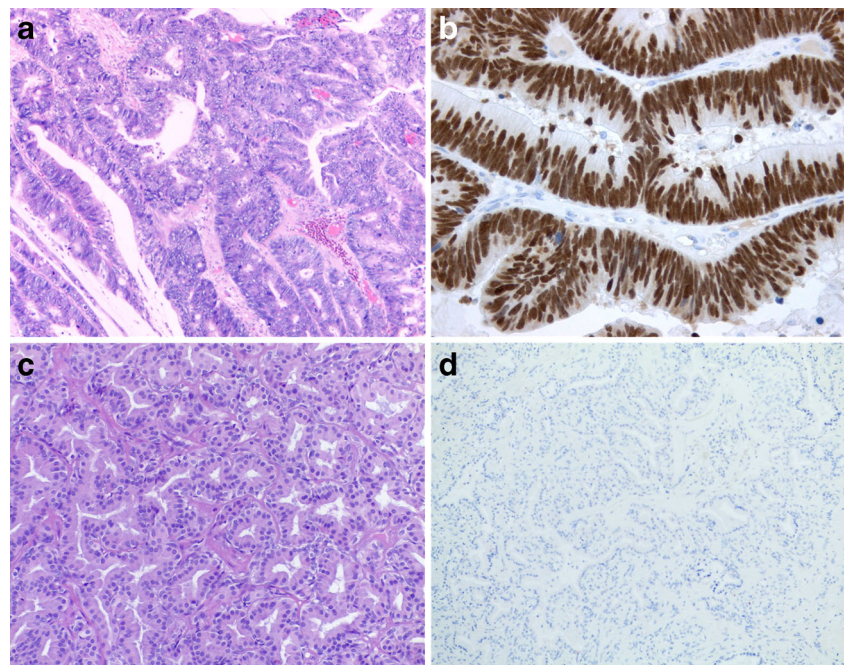
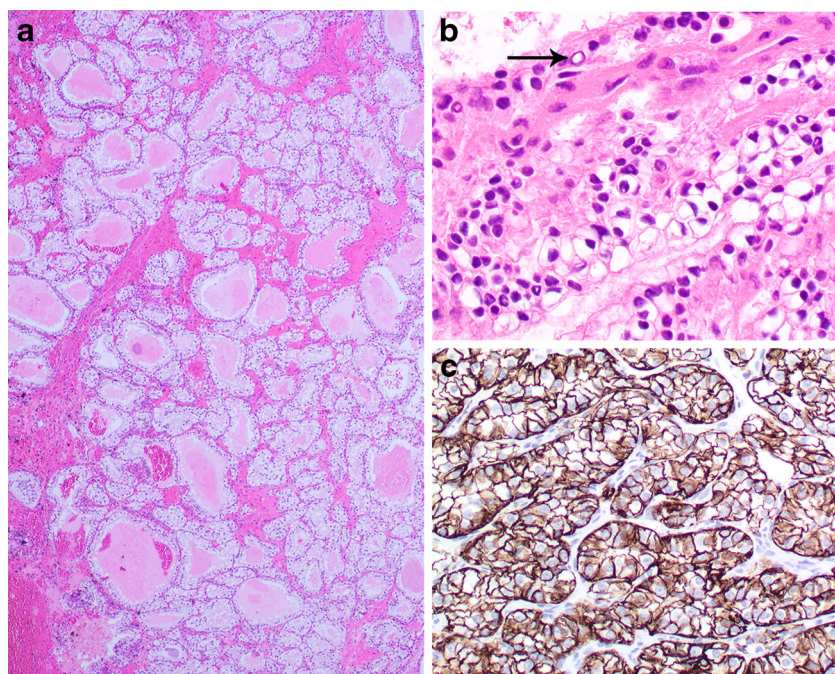


Fig. 6 Sinonasal renal cell-like adenocarcinoma. The neoplastic cells show cleared cytoplasm and a “follicular” pattern with extravasated erythrocytes (a). The cells are small with round nuclei, often showing an intranuclear “vacuole” (arrow) (b). The neoplastic cells show a strong reaction with CAIX (c)



mucous production, either extra- or intracellular, including a signet ring morphology. The survival is variable and it is related to the histologic grade.

Since the 3rd edition was published, more cases have been studied at the molecular level. The most frequently detected alterations are *TP53* mutation and alteration of *CDKN2A* [49–51]. *KRAS* mutations have been reported in 6–40% of the cases, while *BRAF* mutations are detected in <10% [52–54]. *EGFR* mutations and amplifications are observed in a minority of cases [52, 53, 55].

Low grade non-intestinal-type adenocarcinoma must be kept separated from other non-salivary-type sinonasal adenocarcinomas since they have an excellent prognosis, with only rare local recurrence. Histologically, they have a tubulo-glandular or papillary architecture and are composed of cuboidal to columnar cells with only focal mild atypia (Fig. 5). In this new edition, it is recognized that rare cases may histologically resemble metastatic renal carcinoma and such examples are designated as sinonasal renal cell-like adenocarcinoma (Fig. 6) [56–58]. They have a distinctive histologic appearance, being composed of a uniform population of cuboidal to columnar cells with glycogen-rich clear cytoplasm without mucin production (Fig. 6). The neoplastic cells are strongly positive with CK7 and CAIX, but negative with PAX-8 and RCC.

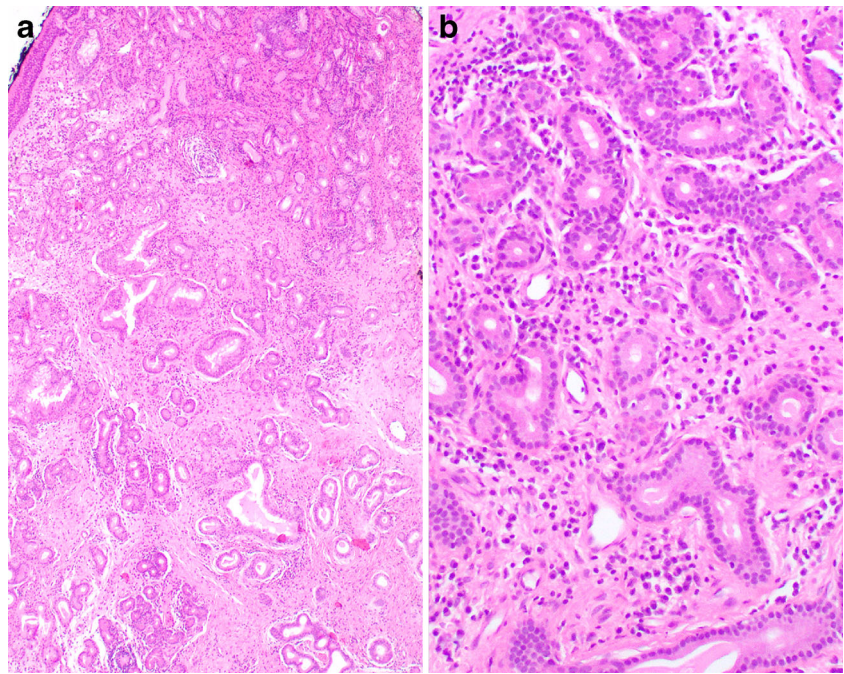
The group of high-grade non-ITAC is histologically very heterogeneous, both cytologically and architecturally, but cellular pleomorphism, brisk mitotic activity, necrosis, and infiltrative growth are common features in all cases [59]. Thus, it is likely that high-grade non-ITAC does not represent a distinct entity, but rather a collection of several different adenocarcinoma types, and that in the near future, it will need

further characterization, no doubt with the aid of molecular techniques.

Sinonasal papilloma: inverted, oncocytic, and exophytic types

One of the major tenants of the new edition was to eschew all eponyms if possible. Thus, Schneiderian papillomas (named after Konrad Viktor Schneider, 1614–1680) were reclassified as sinonasal papillomas, while still maintaining the three major subtypes: inverted, oncocytic, and exophytic, identical subtypes as used in the previous edition [60]. There were updates on the etiology as it relates to human papillomavirus serovars (low-risk versus high-risk serovars), inclusion of information regarding activating mutations in the *EGFR* gene, and the unique histologic appearance of the oncocytic type. Even though a benign tumor, various staging systems using the extent of disease as measured by radiographic or endoscopic findings may be employed [61, 62]. Recent studies have suggested malignant association is a synchronous rather than a metachronous finding [63]. In order to be certain dysplasia or carcinoma is not overlooked, thorough histologic review of all submitted material is recommended. Overall, the histologic features, anatomic distribution and prognosis, and predictive factors remained similar to the previous edition. The key histologic features to keep in mind are the presence of a multilayered epithelium, often showing a ciliated columnar epithelial surface layer and showing well-developed transepithelial migration of neutrophils with the development of microabscesses with mucinous debris [64–66].

Fig. 7 At low power, seromucinous hamartoma presents a lobular architecture and consists of small gland-like structures devoid of atypia (a). At higher power, small glands and tubules are lined by a single layer of cuboidal cells without surrounding myoepithelial cells (b)



Respiratory epithelial lesions

Under this new heading, the WHO classification includes two rare benign acquired lesions of the sinonasal tract, respiratory epithelial adenomatoid hamartoma (REAH) and seromucinous hamartoma (SH) [12, 13]. Indeed, cases presenting histologic features of both REAH and SH have been reported, suggesting that they may represent a spectrum of the same lesion rather than different entities [67]. It still remains to be determined whether they are of neoplastic or non-neoplastic nature, although the presence of an increased fractional allelic loss in REAH supports the hypothesis of a benign neoplasm [68].

Both lesions occur mainly in adult patients and arise predominantly from the posterior nasal septum. Histologically, REAH is composed of gland-like structures arising in continuity with the surface epithelium, lined by multilayered ciliated respiratory epithelium, often with admixed mucous producing cells. These glands are characteristically surrounded by a thick eosinophilic basement membrane. Squamous metaplasia, as well as osseous or cartilaginous metaplasia can be present. The term chondro-osseous respiratory epithelial hamartoma has been used to report such cases. An inflammatory background is also frequently observed.

SH consists of a proliferation of small glands and tubules lined by a single layer of cuboidal cells, organized in clusters and lobules (Fig. 7). These are intermixed with the pre-existing seromucinous glands of the nasal mucosa, often in relationship with invaginated surface respiratory epithelium gland-like structures that resemble REAH. Myoepithelial cells are usually not recognized around the proliferating glands.

Chondromesenchymal hamartoma

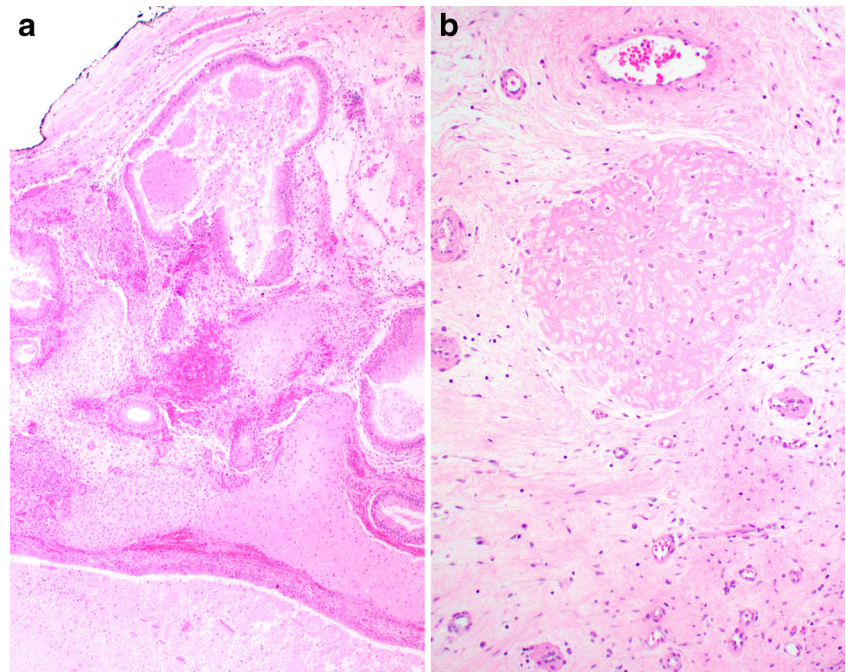
This mesenchymal hamartomatous lesion is included for the first time in the WHO classification [15], although it has been recognized as a distinct entity two decades ago [69]. It occurs predominantly in infants, with involvement of the paranasal sinuses, nasal cavities, and orbit. The behavior is benign, but local invasiveness with intracranial extension through the cribriform plate is described. Sinonasal chondromesenchymal hamartoma is associated with the pleuropulmonary blastoma tumor predisposition disorder, which is due to germline or somatic mutations of the *DICER* gene [70]. It consists of variably sized nodules of hyaline cartilage, set within a stromal component of spindle cells (Fig. 8). The latter can be loose and myxoid or very cellular, with recognizable mitotic figures. Bony trabeculae surround the cartilage nodules and epithelial as well as mature adipose tissue components may also be present [71].

Malignant soft tissue tumors

Biphenotypic sinonasal sarcoma

It is quite uncommon in the twenty-first century to get new entities added to the WHO classification, but biphenotypic sinonasal sarcoma (BSNS) [14], formerly low-grade sinonasal sarcoma with neural and myogenic features, is just such a new tumor. No doubt this newly recognized tumor was previously diagnosed as one of the tumors within the current differential

Fig. 8 Chondromesenchymal hamartoma. At low power, multiple nodules of cartilage are set in a fibromyxoid background, with presence of dilated glands (a). High-power detail of a cartilage nodule surrounded by fibrous tissue (b)



diagnosis: fibrosarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, cellular schwannoma, or synovial sarcoma [72–75]. The distinctive histologic, immunohistochemical, and molecular features, most commonly the recurrent *PAX3-MAML3* gene fusion allow for this tumor to be separated from these histologic mimics [76, 77].

BSNS affects females more often than males (2:1), with a presentation in the 6th decade [76, 78, 79]. Any site may be affected, although the superior nasal cavity and ethmoid

sinus is more commonly affected by a tumor about 4 cm in average greatest dimension. The distinctive histologic features include a bland, spindle cell proliferation arranged in fascicles below an intact, proliferative surface epithelium (Fig. 9). The invaginations of squamous or respiratory-type epithelium may mimic a sinonasal papilloma or a synovial sarcoma (Fig. 9). The nuclei are elongated and slender. Mitoses are inconspicuous and necrosis is not appreciated. Infiltration into adjacent tissues, including bone is common

Fig. 9 Biphenotypic sinonasal sarcoma consists of elongated fascicles of bland appearing spindle cells infiltrating the bone (a). Entrapped gland-like structures derived from the surface epithelium accompany the proliferation (b). Tumor cells are variably positive for S100 protein (c) and smooth muscle actin (d)

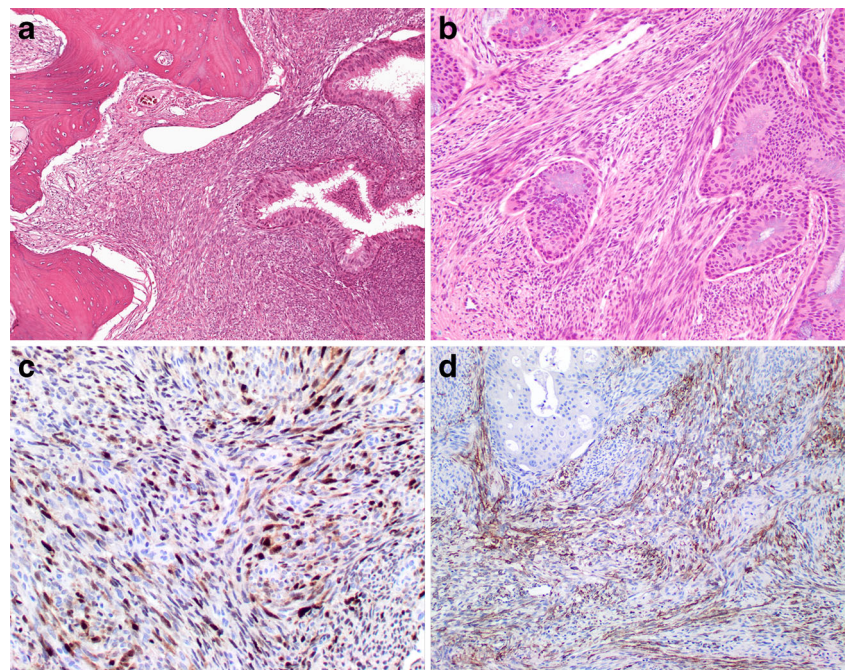
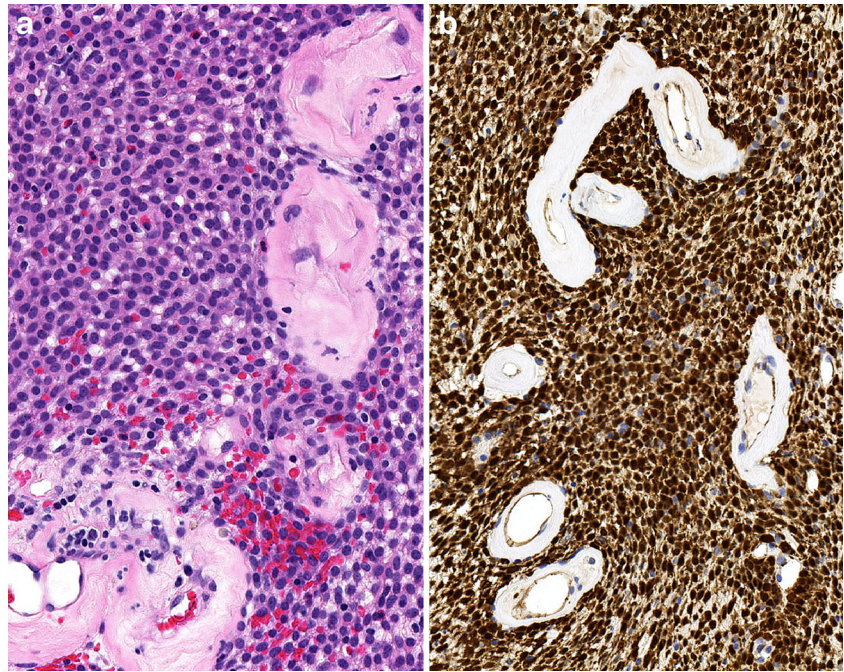


Fig. 10 Glomangiopericytoma is formed by a uniform population of ovoid cells with scanty eosinophilic cytoplasm and characteristically contains vessels surrounded by a thick hyaline membrane (a). The presence of somatic mutations in the *CTNNB1* gene results in diffuse and strong nuclear β -catenin immunoreactivity (b)



[76, 78, 79]. Uncommonly, a hemangiopericytoma-like vascular pattern is seen, while focal rhabdomyoblastic differentiation may be identified (the latter often associated with an alternate fusion partner) [79]. The neoplastic cells will show a focal, patchy to diffuse (i.e., variable) immunoreactivity with S100 protein, SMA, or MSA (Fig. 9), but are negative with SOX10. Focal desmin, MYOD1 and myogenin (in rhabdomyoblastic areas), and isolated keratin and EMA-positive cells may be seen [76, 79]. The characteristic translocation t(2;4)(q35;q31.1) yields the *PAX3-MAML3* fusion transcript [77], while the tumors with rhabdomyoblastic features may harbor *PAX3-FOXO1* and *PAX3-NCOA1* fusion genes [79–81]. Tumors commonly develop recurrence (50%), but distant metastases and death from disease have not been reported thus far [76].

Synovial sarcoma

Synovial sarcoma (SS) was previously included in the hypopharynx chapter, where it received only a cursory paragraph. In the current edition [82], there is an expanded coverage of the topic, but it is included in the sinonasal tract primarily as a differential diagnostic consideration for biphenotypic sinonasal sarcoma (BSNS). The skull base and neck are occasionally affected, where the monophasic or biphasic subtypes may be seen. One of the helpful findings is a strong TLE1 nuclear immunoreactivity, patchy reactivity with EMA, and cytokeratins (CK7), while usually negative for S100 protein and SMA. The characteristic chromosomal translocation t(X;18)(p11;q11), results in a gene fusion between *SYT* and *SSX* genes, distinctly different from BSNS [83, 84].

Borderline soft tissue tumors

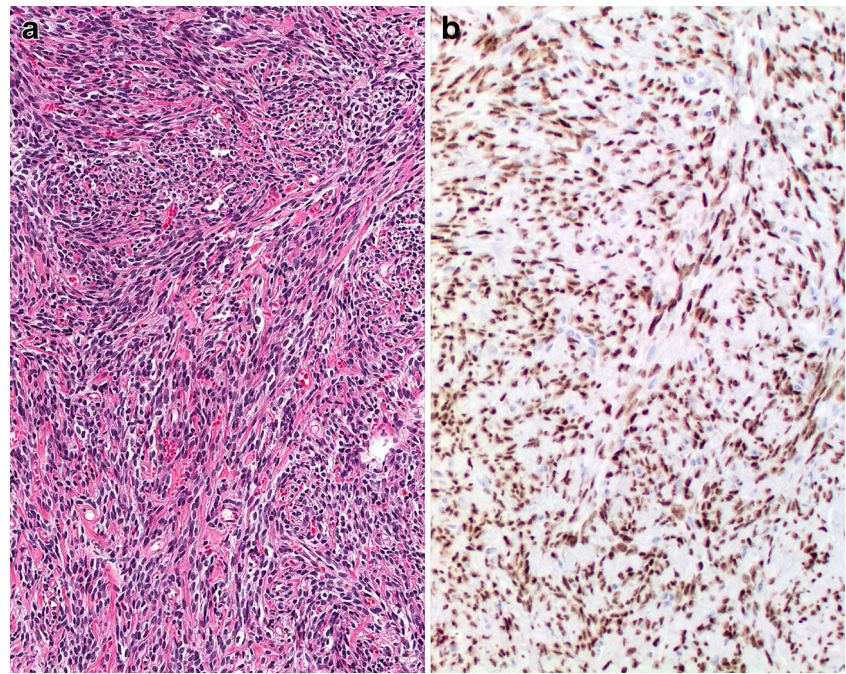
Desmoid-type fibromatosis

Desmoid-type fibromatosis, a locally infiltrative, non-metastasizing cytologically bland (myo)fibroblastic neoplasm [85], has recently been recognized to be associated with *CTNNB1* (β -catenin encoding gene) mutations in up to 85% of sporadic cases [86–88], while Gardner-type FAP syndrome-associated tumors show germline mutations of the APC gene [89–91]. The changes in *CTNNB1* gene yield a very strong nuclear β -catenin expression by immunohistochemistry [92–94]. The tumors are cellular, showing a fascicular growth with moderate cellularity of spindled cells that have tapered nuclei with a syncytial cytoplasm set within a variably collagenized stroma.

Sinonasal glomangiopericytoma

A sinonasal tumor demonstrating perivascular myoid phenotype [85], glomangiopericytoma, was included in the previous edition, but additional findings were incorporated into the current edition [95–97]. The tumors are unencapsulated, submucosal patternless proliferations, arranged in short fascicles and storiform to short palisades of a syncytial closely packed spindled cell proliferation. A prominent, thick, acellular peritheliomatous hyalinization of the richly vascularized neoplasm is quite characteristic (Fig. 10). The neoplastic cells show a strong reaction with actins (smooth muscle > muscle specific), nuclear β -catenin (Fig. 10), and cyclin-D1, without any significant expression of CD34, CD31, CD117, STAT6,

Fig. 11 This solitary fibrous tumor is composed of a population of bland spindle cells associated with collagen matrix production (a). As a result of a *NAB2-STAT6* translocation, neoplastic cells show diffuse STAT6 nuclear positivity (b)



bcl-2, keratins, desmin, or S100 protein [95, 96, 98]. Similar to desmoid-type fibromatosis, glomangiopericytoma shows somatic, single nucleotide mutations in the *CTNNB1* gene that encodes β -catenin [96, 97], which results in nuclear accumulation of β -catenin (detected by immunohistochemistry) and shows up-regulation of cyclin D1 [96]. Especially helpful in the differential is a lack of *NAB2-STAT6* gene fusion, a feature of solitary fibrous tumor [99].

Solitary fibrous tumor

In the 3rd edition, solitary fibrous tumor was almost a diagnosis of exclusion, requiring a combination of architectural, histochemical, and immunohistochemical findings, that showed morphologic overlap with several other tumors in the SNT. Recent studies have elaborated the fusion gene associated tumor of fibroblastic phenotype that shows a branching vascular pattern to be associated with a fairly unique and specific *NAB2-STAT6* fusion [85, 100–102]. This bland spindle cell proliferation usually shows stellate to staghorn-like vessels associated with a variable collagenous background (Fig. 11). Unique from other tumors in the differential diagnosis, there is a strong CD34 and nuclear STAT6 reaction (Fig. 11), but a lack of reactivity with desmin, S100 protein, actins, and nuclear β -catenin [99, 103, 104].

Epithelioid hemangioendothelioma

In keeping with the newly identified, translocation-associated neoplasms, epithelioid hemangioendothelioma was included in this edition of the classification [85]. The head and neck is

rarely affected [105–108] by this slow-growing, infiltrative tumor that frequently shows lymph node metastasis [108]. The tumors often show a multinodular appearance macroscopically, with both an epithelioid and histiocytoid appearance to the endothelial cells arranged in cords and strands of cells that exhibit subtle intracytoplasmic lumina within the ample eosinophilic cytoplasm. Profound nuclear pleomorphism is seen in up to 30% of cases. A myxohyaline stroma is seen in the background, while mitoses are sparse [105, 106, 108–110]. Although various endothelial markers are usually positive (CD31, ERG, FLI1), keratin expression is present in about 30% of cases, resulting in misclassification [108, 109]. There is usually a *WWTR1-CAMTA1* present in most of the cases, with a subset of cases showing a *YAP1-TFE3* fusion [107, 108, 111, 112]. Tumors are generally indolent, although tumors with >3 mitoses/50 HPFs and tumors >3 cm show higher mortality [105, 109, 110].

Hematolymphoid tumors

Any hematolymphoid neoplasm may develop within the sinonasal tract, but for classification purposes, the extranodal natural killer (NK)/T cell lymphoma, nasal type (ENKTLNT) has a specific predilection for the sinonasal tract, a cytotoxic phenotype, and a universal association with Epstein-Barr virus (EBV) [113–118]. Overall, lymphomas represent the third most common malignancy of the SNT tract [119, 120]. ENKTLNT has a strong predilection for East Asians and Latin Americans [114–116], but has increased in other countries [114]. There is involvement of the nasal cavity and

paranasal sinuses, although other extranodal sites may be affected. The clinical presentation usually begins non-specifically, simulating chronic rhinosinusitis, but eventually progresses to perforation, ulceration, and even extension into the soft tissues and skin of the face. Arranged in an angiocentric and angi-destructive/invasive pattern, there is usually significant geographic necrosis, often obscuring the underlying viable tumor cells. The neoplastic cells are quite variable, but show irregular contours, folds, and grooves, with increased mitoses. There is usually CD3 and other cytotoxic markers (TIA-1, granzyme B, perforin) immunoreactivity, while CD56 is seen more often in NK cell tumors [121–124] and CD30 is seen in large cell morphology lesions. CD57 is nearly always negative [121, 122]. There is nearly universal EBV detection by in situ hybridization [125–127], with tumors that lack EBER, considered peripheral T cell lymphoma, unspecified [126, 128]. The *JAK/STAT* pathway is activated in the majority of ENKTLNT, as a result of genetic alterations of *JAK3*, *STAT3*, or *PTPRK* [129–132].

Neuroectodermal/melanocytic tumors

Ewing sarcoma/primitive neuroectodermal tumors

There was no specific change in the diagnostic criteria of this high-grade primitive small round cell sarcoma that shows variable neuroectodermal differentiation [133–136]. However, Ewing sarcoma, classically defined by the presence of a translocation between *EWSR1* gene on chromosome 22 and the *FLII* gene on chromosome 11, is well-known to increasingly show greater diversity in the translocation partners, and even perhaps showing similar morphology, but a completely different molecular profile and often associated with a unique histologic appearance (such as adamantinoma-like) [137, 138]. Importantly, these tumors usually show a strong and diffuse membranous immunoreactivity with CD99, while FLII and ERG show nuclear reactions when the fusion partner is *FLII* or *ERG*, respectively [139–141]. Focal to diffuse and weak to strong cytokeratin reaction may be seen, although more frequently in the adamantinoma-like Ewing family tumors [136, 138, 142]. At present, *EWSR1*-negative cases may show the *CIC-DUX4* fusion, the result of t(4;19) or t(10;19) translocation [143], but these tumors show variable CD99 expression and nuclear heterogeneity and are usually soft tissue tumors of the extremities [144].

Olfactory neuroblastoma

The neuroectodermal tumors are sometimes very difficult to characterize. Olfactory neuroblastoma is a malignant neuroectodermal neoplasm with neuroblastic differentiation, most often localized to the superior nasal cavity

[133]. Very uncommon, the tumor seems to show a peak in the 5th–6th decades [145–147], with males affected slightly more often than females (1.2:1). The site of tumor development is stressed for this neoplasm, which must involve the cribriform plate of the ethmoid sinus, part of the superior turbinate (concha), or the superior half of the nasal septum, with other sites of involvement a diagnosis of exclusion (unless recurrent) [148]. Even though there is marked destruction of the olfactory apparatus, anosmia is only reported in <5% of patients. Imaging must be incorporated into the interpretation, with the classic “dumbbell-shaped” mass extending across the cribriform plate very helpful. Staging is done by the Kadish [149] or the Morita modified Kadish classification system [150]. Low-grade tumors, with their characteristic submucosal, sharply demarcated lobular architecture of small cells with round to oval nuclei with delicate “salt-and-pepper” chromatin are easily diagnosed, even when fibrillary matrix (neuropil) or rosettes are absent. However, it is higher grade tumors that demonstrate nuclear pleomorphism, nucleoli, tumor necrosis, increased mitoses, and decreased to absent neuropil, which are much more difficult to recognize and diagnose. Melanin pigment, ganglion cells, rhabdomyoblasts, and divergent differentiation as islands of true epithelium (squamous pearls or gland formation), further complicate diagnosis [151–155]. For the vast majority of cases, ONBs show scant or focal to completely absent expression of keratins (including EMA and CAM5.2) [156], but usually show strong and diffuse immunoreactivity with synaptophysin, chromogranin-A, CD56, neurofibrillary protein, and calretinin (nuclear and cytoplasmic) [45]. The sustentacular cells at the periphery of the cell nests are highlighted by both S100 protein and glial filament acidic protein (GFAP). It is this latter finding that may help with separation from other small round blue cell tumors of the SNT that may show histological and immunophenotypic overlap [157]. The prognostic value of the Hyams grading system based on tumor architecture, pleomorphism, neural matrix, mitotic activity, necrosis, and gland/rosette presence was reinforced by inclusion in the chapter [158–161]. Recent work suggests that the sonic hedgehog signaling pathway seems to play a role in pathogenesis [162], while *EWSR1* rearrangements are not seen.

Mucosal melanoma

Sinonasal tract mucosal melanoma was updated to include new information specifically regarding molecular mutational status, as the *NRAS* and *KIT* mutations/amplifications are seen with a much higher frequency than *BRAF* mutations, a sharp contrast to cutaneous and uveal primary tumors, resulting in a difference in management and patient outcome [133].

Entities excluded

A number of entities were removed from the nasal cavity, paranasal sinuses, and skull base section, including the following: verrucous carcinoma, papillary squamous cell carcinoma, basaloid squamous cell carcinoma, adenosquamous carcinoma, acantholytic squamous cell carcinoma, all of the malignant salivary gland-type carcinomas, typical carcinoid, myoepithelioma, oncocytoma, inflammatory myofibroblastic tumor, myxoma, chondrosarcoma, osteosarcoma, chordoma, all benign bone and cartilage tumors, diffuse large B cell lymphoma, extramedullary myeloid sarcoma, histiocytic sarcoma, Langerhans cell histiocytosis, melanotic neuroectodermal tumor of infancy, all germ cell tumors, and secondary tumors. It was determined that the histologic features of these entities is sufficiently well described in other parts of the book and duplication served no useful purpose. Further, many of these entities are covered in great detail in their respective books on the topic (bone, cartilage, soft tissue, central nervous system, and lymph node and hematolymphoid tumors).

Compliance with ethical standards

Conflict of interest All authors have contributed to this work and they declare that there are no financial conflicts associated with this study.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable.

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