Poorly differentiated sinonasal tract malignancies: A review focusing on recently described entities

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SUMMARY

Sinonasal tract malignancies are uncommon, representing no more than 5% of all head and neck neoplasms. However, in contrast to other head and neck sites, a significant proportion of sinonasal neoplasms tend to display a poorly/ undifferentiated significantly overlapping morphology and a highly aggressive clinical course, despite being of diverse histogenetic and molecular pathogenesis. The wide spectrum of poorly differentiated sinonasal epithelial neoplasms with small "basaloid" blue cell morphology includes basaloid squamous cell carcinoma (both HPV+ and HPV-unrelated), nasopharyngeal-type lymphoepithelial carcinoma (EBV+), small/large cell neuroendocrine carcinoma, esthesioneuroblastoma, poorly differentiated carcinoma of salivary type (myoepithelial carcinoma and solid adenoid cystic carcinoma), NUT midline carcinoma, the recently described SMARCB1-deficient sinonasal carcinoma, sinonasal teratocarcinosarcoma and, as a diagnosis of exclusion, sinonasal undifferentiated carcinoma (SNUC). On the other hand, a variety of sarcomas, melanoma and haematolymphoid malignancies have a predilection for the sinonasal cavities, and they occasionally display aberrant cytokeratin expression and show small round cell morphology thus closely mimicking poorly differentiated carcinomas. This review summarizes the clinicopathological features of the most recently described entities and discuss their differential diagnosis with emphasis on those aspects that represent pitfalls.

Keywords: sinonasal tract – SNUC – small round cell tumor – NUT midline carcinoma; SMARCB1-deficient carcinoma – esthesioneuroblastoma

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Unlike any other body site or organ, the sinonasal cavities are notorious for being the origin of histogenetically, genetically and biologically highly diverse neoplastic disease entities, an observation that is very surprising given the relatively small proportion of this anatomic region in relation to the total body area (1). Except for conventional squamous cell carcinoma (SCC) and intestinal-type sinonasal adenocarcinoma, the plethora of neoplastic entities in the sinonasal tract and their rarity is only comparable to that of soft tissue sarcomas with every second encountered neoplasm likely being of a different type. This and the fact that sinonasal tract malignancies as a group represents no more than 1% of all malignant neoplasms and 5% or less of head and neck cancers, familiarity with them is generally limited and, thus, the diagnostic workup and exact classification of them pose a real diagnostic challenge in surgical pathology practice necessitating sufficient familiarity with and knowledge of their phenotypic diversity and specific diagnostic criteria. This is further complicated by the fact that poorly differentiated neoplasms at this site frequently display significant morphological and/or phenotypic overlap. Furthermore, diagnosis of some entities relies on demonstration of either specific genetic aberrations (SMARCB1-deficient carcinomas and NUT midline carcinomas) or of a specific infectious agent (EBV or HPV). In this review the pertinent clinicopathological features of the poorly differentiated sinonasal neoplasms and their mimics are discussed with emphasis on aspects that might represent diagnostic challenges or pitfalls.

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SINONASAL BASALOID EPITHELIAL NEOPLASMS

Sinonasal basaloid squamous cell carcinoma and variants

In contrast to conventional SCC which represents the most common carcinoma type in the sinonasal cavities (60%) (2,3), basaloid SCC of the sinonasal tract comprises no more than 5% of head and neck basaloid SCC. The behavior of head and neck basaloid SCC showed site-dependent variation among different studies (4). Although generally considered highly aggressive, recent studies showed survival characteristics comparable to conventional SCC or even paradoxically better than it (4). This variation according to site among other clinicopathological parameters suggests heterogeneity of neoplasms in the generic category of head and neck basaloid SCC. Recent studies illuminated this aspect thereby resulting in splitting of several variants previously included at least in part in this basaloid category (5). Among the latter are HPV-related basaloid SCC with its excellent response to multimodal radiochemotherapy and hence a better outcome compared to conventional basaloid SCC on one hand and the NUT midline carcinoma with its almost universal radio/ chemoresistance and hence dismal outcome on the other hand. Between the two ends of the spectrum are heterogeneous neoplasms including in particular SMARCB1-deficient basaloid carcinoma with generally good but very variable outcome after aggressive treatment regimens. Thus it is mandatory to exactly subtype sinonasal neoplasms traditionally fitting the basaloid SCC line of differentiation. Conventional basaloid SCC is identical to its other head and neck counterparts and is frequently associated with surface epithelial dysplasia (Fig. 1).

A recently reported variant of HPV-associated basaloid sinonasal carcinoma showed a strict sinonasal location among other head and neck sites and adenoid cystic carcinoma-like morphology and/or immunophenotype (6,7). This rare variant can be distinguished from true salivary adenoid cystic carcinoma by

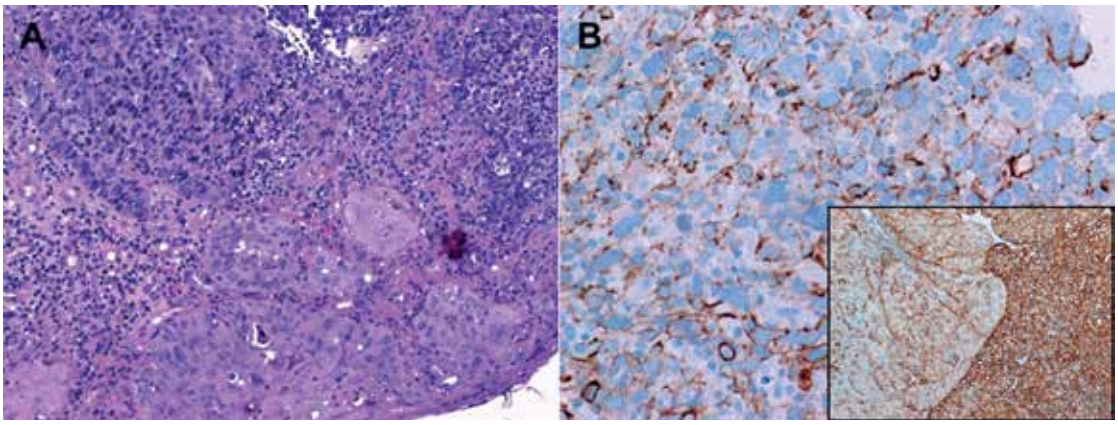

Fig. 1. Conventional basaloid SCC of the sinonasal tract (**A**, upper field) associated with dysplastic surface epithelium. **B**: Cytokeratin 5/6 may show perinuclear pattern closely resembling the pattern of pan-CK seen in SCNEC (main image), but the tumor lacks any neuroendocrine marker reactivity. Subimage: overview of CK5/6 showing basaloid component (left) abutting conventional SCC component (right).

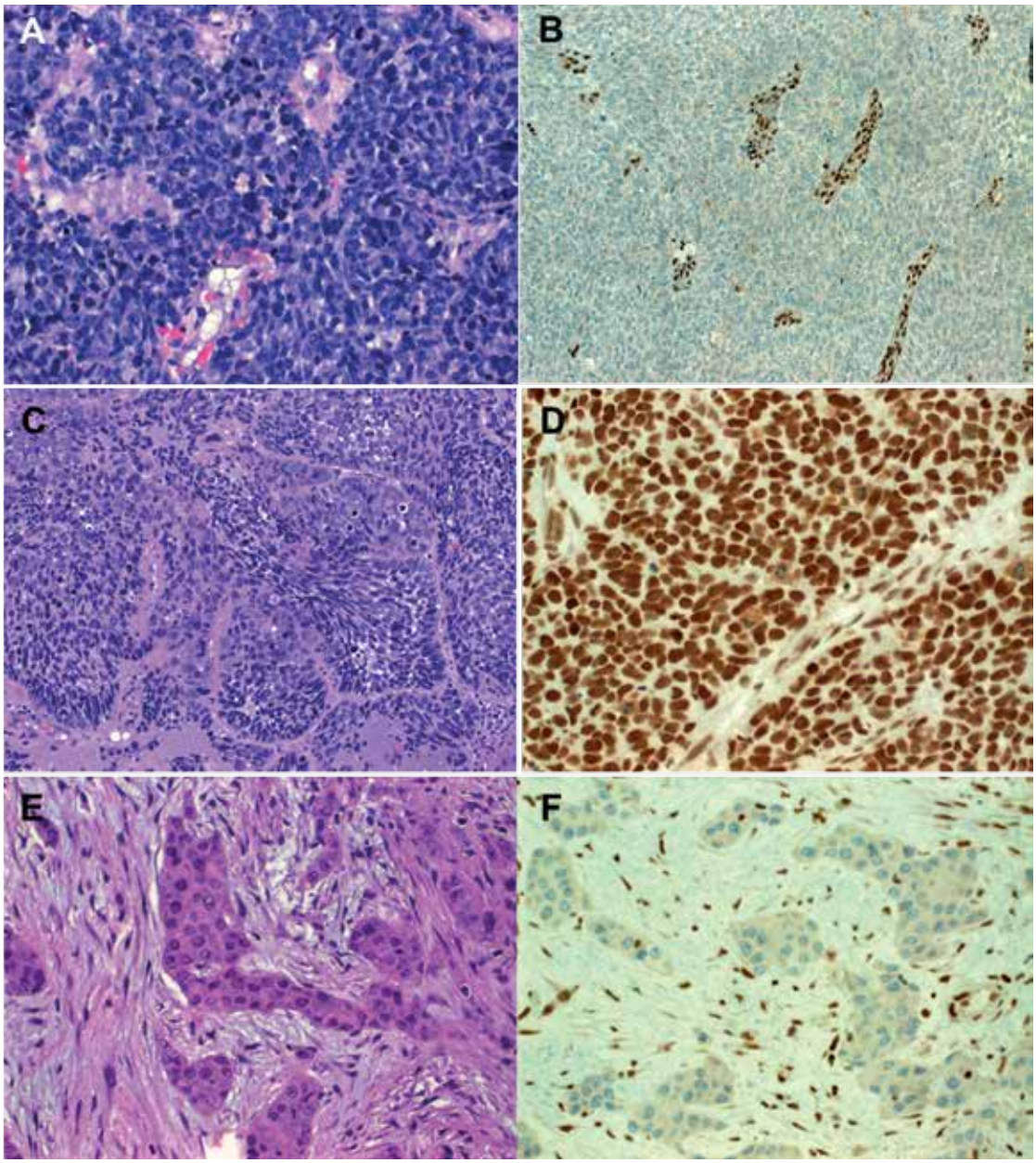

Fig. 2. SMARCB1-deficient sinonasal carcinoma with the prototypical basaloid blue cell pattern (**A**) and complete loss of SMARCB1 (**B**). In contrast, conventional basaloid SCC (**C**) showed intact nuclear SMARCB1 (**D**). Rare examples of SMARCB1-deficient carcinoma with eosinophilic squamoid cell pattern but no keratinization (**E**), complete loss of SMARCB1 in same case (**F**).

frequent occurrence of dysplastic surface epithelium, uniform presence of HPV by molecular methods and absence of MYB gene fusions in contrast to the reverse findings in adenoid cystic carcinomas (7).

Sinonasal NUT midline carcinoma (NMC)

This exceptionally rare highly aggressive carcinoma variant was originally described in 1991 as a pediatric thoracic (thymic) malignancy (8). Genetic analysis reveals a translocation involving chromosome 15 and 19 which results in fusion of nuclear protein in testis (*NUT*) to the promodomain containing 4 (*BRD4*) gene (9,10). Mainly children and young adults are affected with an age range of 0-78 years (half of patients are young adults). The vast majority of reported cases originated in the respiratory tract or within the thoracic cavity (thymus). Notably, half of reported cases originated at head and neck sites with almost half of them being of sinonasal tract origin (nose and/or sinuses) (9,11,12). This rare sinonasal carcinoma entity is notorious for its highly aggressive behavior with fatal rapid progress under intensive multimodal therapy. The vast majority of NMC patients with extended follow-up died within one year irrespective of aggressive multimodal therapy.

The histology of NMC is not specific or pathognomonic although some features might be helpful as a clue to think of this entity. Generally, the tumors are composed of variably thick communicating trabeculae and strands of monotonous small to medium-sized dark staining basaloid undifferentiated cells set within a desmoplastic stroma (9,11,12). This appearance is essentially not distinguishable from the majority of cases of the recently reported SMARCB1-deficient sinonasal carcinoma (see section on this entity below). However, in contrast to the former, NMC frequently show foci of frank squamous differentiation which might be highly maturing and abrupt abutting the undifferentiated "blue cells". Indeed, this type of

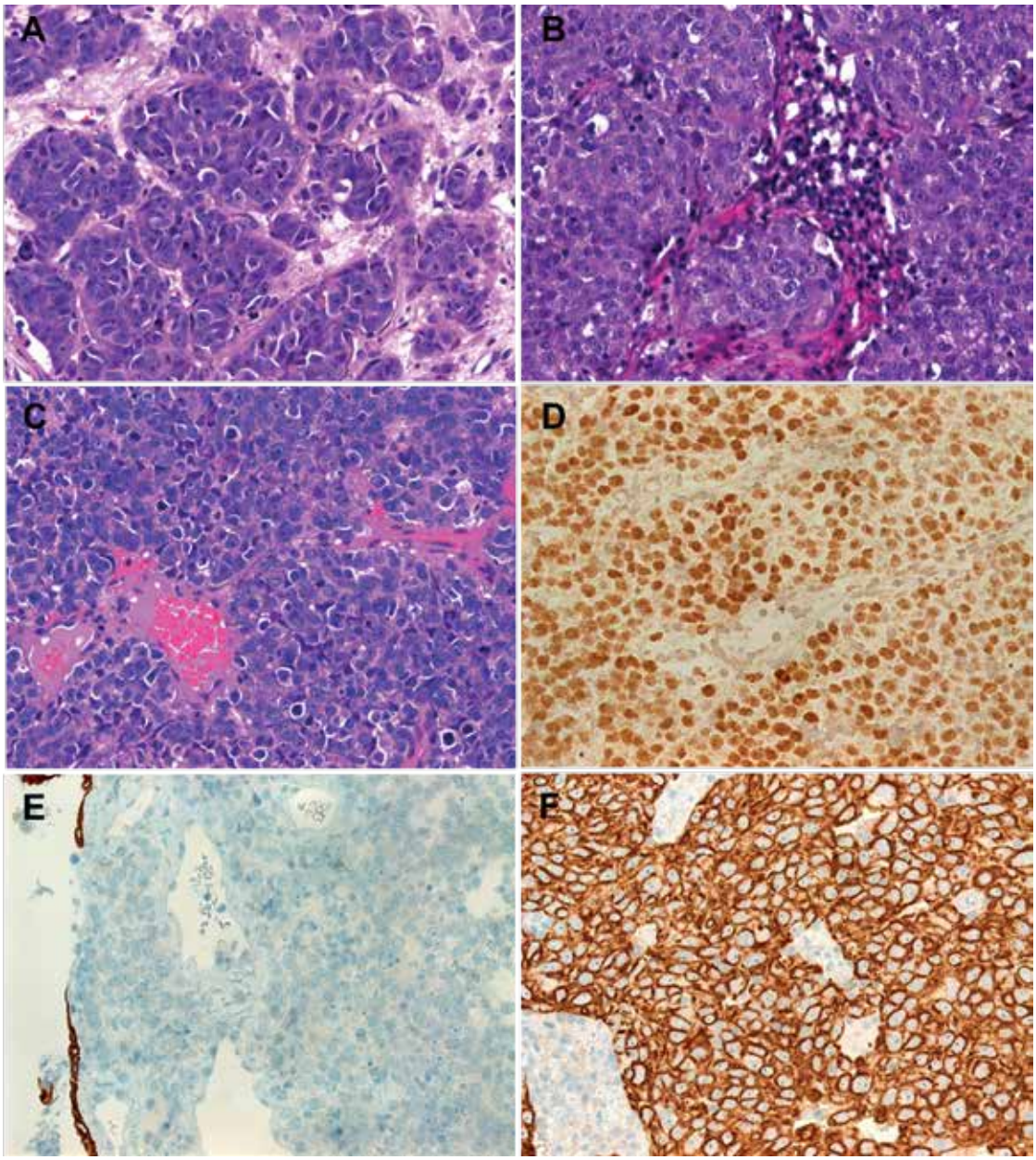

Fig. 3. SNUC cases display nested (**A**) or diffuse (**C**) growth of large anaplastic cells with prominent nucleoli and absent expression of CK5/6 (E). Similar pattern as SNUC seen in a case of lymphoepithelial carcinoma with subtle inflammatory reaction (**B**), but strong positivity for EBER1/2 (EBV) by in situ hybridization (**D**). In contrast to typical SNUC, lymphoepithelial carcinoma shows strong expression of CK5/6 (F).

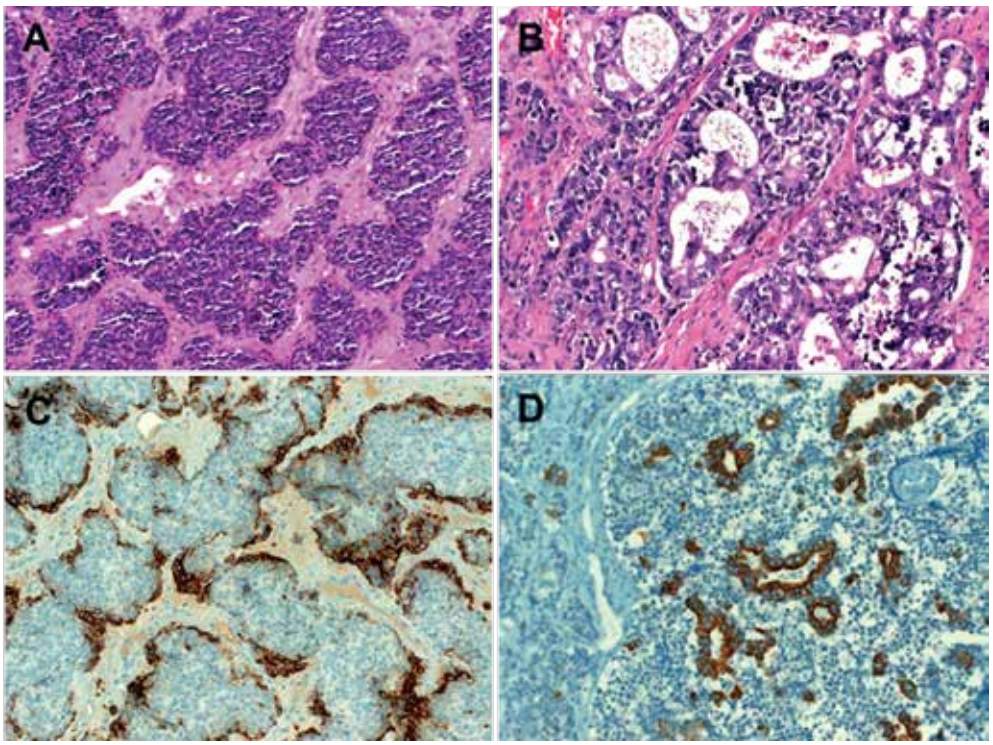

Fig. 4. Several neoplasms classified as high-grade non-intestinal adenocarcinoma frequently show foci similar to esthesioneuroblastoma (**A**) associated with glandular component (**B**). Synaptophysin highlighted peripherally located cell aggregates that were positive for calretinin as well suggesting limited olfactory-like differentiation (**C**). Strong expression of pancytokeratin limited to glands indicates true epithelial differentiation (**D**).

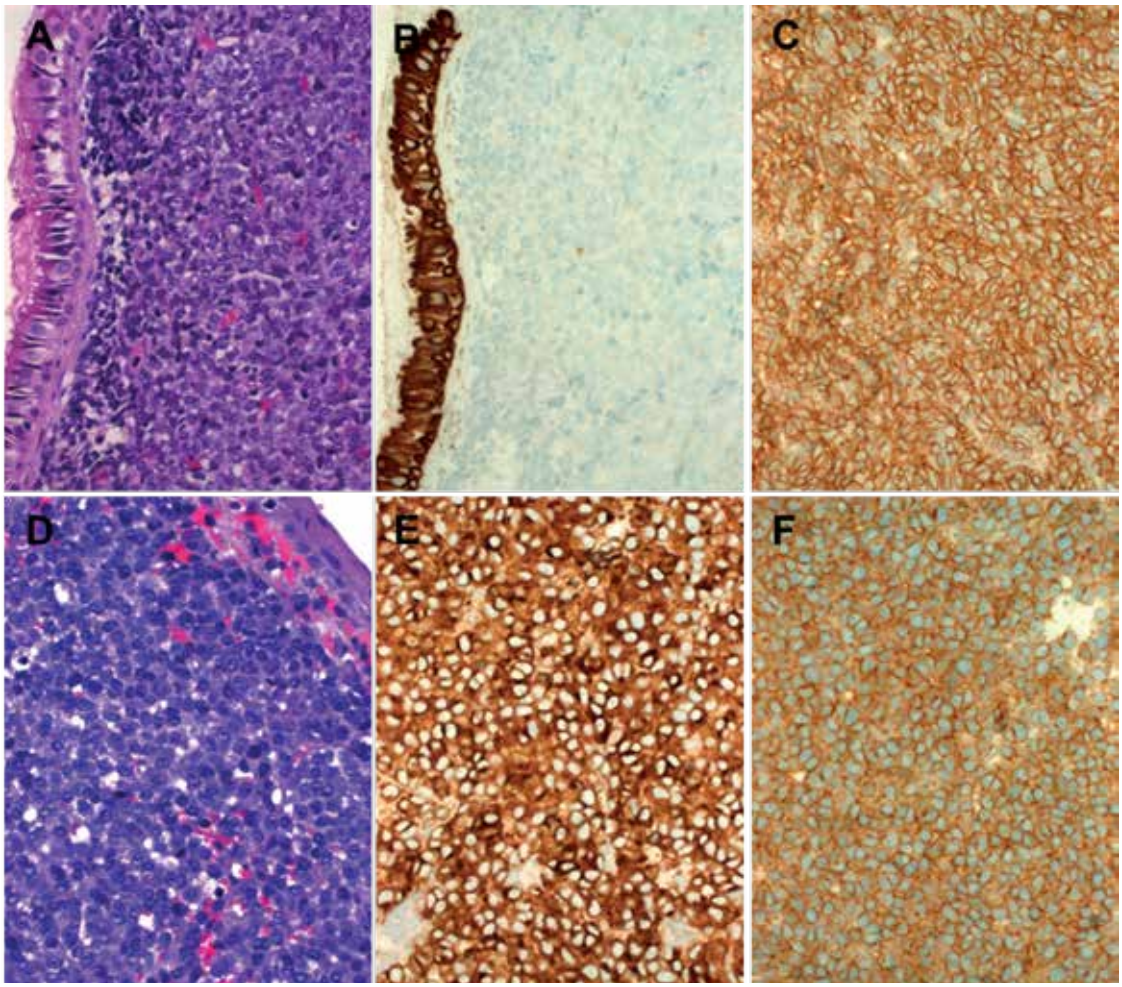

Fig. 5. This example of conventional sinonasal Ewing sarcoma (**A**) lacked any specific line of differentiation (**B**, pan-CK) and strongly expressed CD99 in membranous pattern (**C**). This case was confirmed by EWSR1-FISH. Small cell variant of sinonasal amelanotic melanoma growing beneath metaplastic surface epithelium (**D**) with strong expression of pan-melanoma cocktail (**E**) and moderate membranous expression of CD99 which could be mistaken for Ewing sarcoma (**F**).

squamous differentiation might have represented a major factor in under-recognizing this entity by many general surgical pathologists who are not aware of the entity and those who do not include NUT immunostaining in this differential diagnostic context or have no access to molecular testing. The limited electron microscopic studies showed features of epithelial differentiation with some cases consistent with squamous cells but no evidence of glandular differentiation has been seen (9). Rare cases showed heterologous elements, mainly chondroid differentiation.

IHC is consistent with epithelial (squamous) differentiation with frequent expression of low molecular weight cytokeratins, p63 and absence of other specific myoepithelial, myogenic, neuroendocrine and melanocytic markers (9,11,12). Definitionally, NMC lacks oncogenic EBV and HPV infections. NUT IHC can be used as a screening method using currently available polyclonal and monoclonal antibodies with a sensitivity of 80% and 87% and a specificity of 96% and 100%, respectively as compared to molecular testing by FISH methods (10). One third of cases carry a variant NUT translocation (BRD3, etc.) (10).

SMARCB1-deficient sinonasal basaloid carcinoma

Recently, our group and the group of Bishop et al. identified a sinonasal carcinoma variant as being SMARCB1-deficient (13,14). This uncommon variant has been mainly included among basaloid SCC (15) as the vast majority of cases (70%) displayed this stereotypic "blue cell" basaloid pattern. To date less than 30 cases have been reported in the literature (13,14,16,17). Tumors occur mainly in females (2:1) with an age range of 28-78 yrs (mean, 59). The nasal cavity and the sinuses are affected either in combination or in isolation. The full biological potential of this entity remains to be defined in larger future studies but current data suggest a neoplasm with variable intermediate to high aggressiveness and with frequently excellent response to aggressive multimodal therapy.

Following initial description of the stereotypical cases, we have recognized several other non-basaloid variants within the spectrum of this entity including eosinophilic/rhabdoid, oncocytoid, adenoid, squamoid, and small cell carcinoma-like patterns (16) (Fig. 2). While some metastatic neoplasms showed frankly rhabdoid cell features (13), this is usually very subtle and hardly ever recognizable in the primary tumor with a few exceptions. As the name implies, the SMARCB1-deficient sinonasal carcinomas are defined by complete loss of the tumor suppressor SMARCB1 (synonyms: INI1; hSNF5; BAF47) in the tumor cell nuclei while being retained in the background stromal and inflammatory cells as well as the normal epithelium of the mucosa/glands. This variant should be distinguished from primary and metastatic SMARCB1-deficient neoplasms of the head and neck and the skull base (18).

EBV-related lymphoepithelial carcinoma of nasopharyngeal type

This tumor is identical to its nasopharyngeal counterpart both histologically and immunophenotypically except for being located in the sinonasal cavities (1). Detection of the EBV by in situ hybridization is helpful in establishing diagnosis. On occasion, diagnosis of sinonasal nasopharyngeal-type carcinoma might be missed if the lymphoepithelial growth pattern is less obvious (19) (Fig. 3).

Anaplastic myoepithelial carcinoma and solid-pattern salivary analogue neoplasms

A rare example of myoepithelial carcinoma with anaplastic features has been reported by Petersson et al (20). This tumor showed cytomorphology similar to small round cell tumors and its myoepithelial nature was evident only after immunohistochemical analysis which uncovered expression of several of the myoepithelial markers. In addition, several salivary-type neoplasms including in particular adenoid cystic carcinoma may undergo high-grade transformation mimicking anaplastic myoepithelial carcinoma and other basaloid sinonasal tract neoplasms (21,22). Thus thorough sampling of resection specimens, and in case of limited biopsy, consideration of these possibilities and use of a wider immunohistochemical marker panel directed towards these specific entities is mandatory.

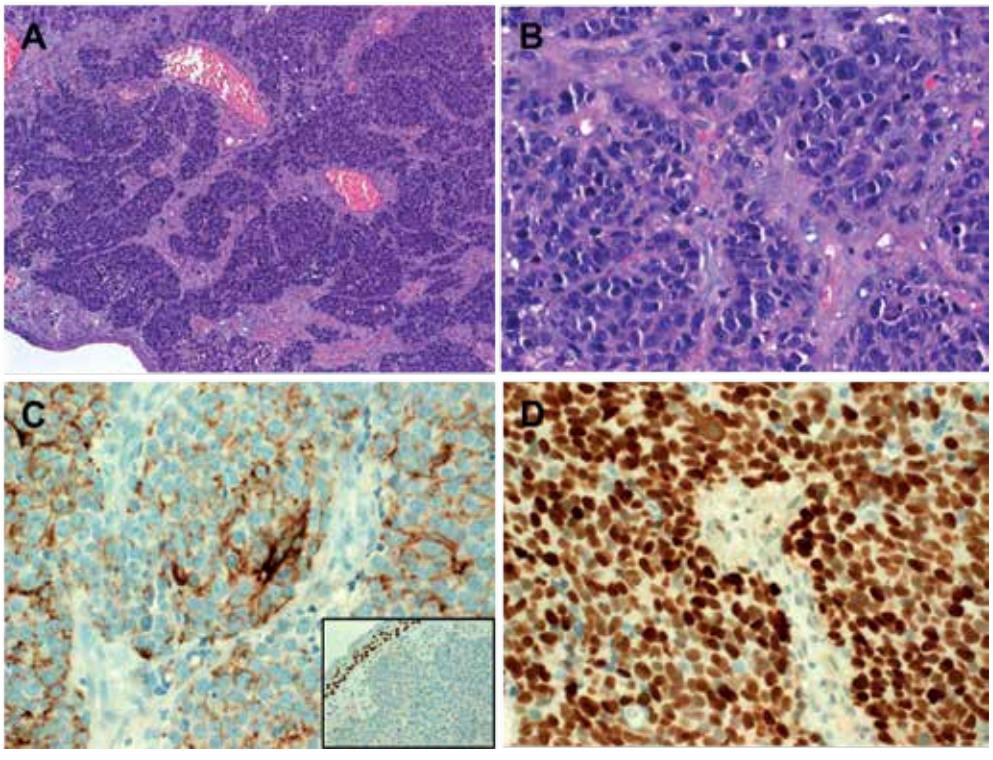

Fig. 6. Several sinonasal neoplasms remain unclassified such as this poorly differentiated small cell non-neuroendocrine carcinoma (**A**) which developed years after irradiation for uveal melanoma. Nested pattern may mimic high-grade esthesioneuroblastoma (**B**). Pancytokeratin showed diffuse perinuclear pattern with focal abortive gland-like/rosette-like accentuation (**C**, main image). P63 was negative in the tumor cells (**C**, inset). **D**: almost all of tumor cells expressed TP53 suggesting TP53 mutation.

Sinonasal undifferentiated carcinoma (SNUC): a final pathway of dedifferentiation of histogenetically diverse entities?

Since description of sinonasal undifferentiated carcinoma (SNUC) as a distinctive highly aggressive variant of sinonasal carcinoma by Frierson et al. in 1986 (23), classification of poorly differentiated sinonasal carcinomas has been undergoing a continuous refinement with dynamic splitting of new entities, the last of them is the SMARCB1-deficient carcinoma. Accordingly, the majority of tumors originally reported as SNUC could be currently reclassified as specific genetically or immunophenotypically definable variants such as NUT midline carcinoma (9,11,12), SMARCB1-deficient carcinoma (13,14), anaplastic myoepithelial carcinoma (20), dedifferentiated SCC and others (24,25). The consequence of this is an ever diminishing of the SNUC category which currently represents a diagnosis of exclusion. However, tumors that fit the SNUC category and are not otherwise definable as specific entities still exist (Fig. 3). Based on these and on own observations, it is likely that these "true" SNUC rather represent a final common pathway of dedifferentiation for a variety of sinonasal epithelial neoplasms, in particular for SCC (24,25).

Sinonasal tract ameloblastomas

Variable extension into the sinonasal cavities can be seen in advanced gnathic ameloblastomas and might on occasion represent a source of diagnostic confusion if not thought of. However, a small proportion of all ameloblastomas occur as sinonasal tact primary neoplasms in the absence of a gnathic primary or connection to the gnathic bones. In line with a distinctive subtype of extragnathic ameloblastomas, those originating primarily in the sinonasal tract occur at higher age (mean age, 60 yrs versus 20-40 yrs) with a significant predilection for men (26). To date, there was no report of distant metastases or death from this disease. Origin from pluripotent cells within the basal mucosal layer of the sinonasal tract seems to be the most plausible histogenetic hypothesis and it is supported by uniform presence of connection of the tumor strands to the basal covering mucosa in oriented biopsies (26). The vast majority of sinonasal ameloblastomas are of the plexiform subtype. The differential diagnosis of sinonasal tract ameloblastomas is essentially limited after exclusion of secondary involvement from a gnathic primary. In the experience of the author however, rare sinonasal tract SCC may show ameloblastic/ameloblastoid features to a variable extent, thus closely mimicking ameloblastoma or, due to invariable presence of clear-cut atypia, dedifferentiated ameloblastoma/ameloblastic carcinoma. The nosologic significance and/or molecular distinctness of these rare SCC variants and their relationship, if any, to genuine ameloblastic carcinomas remain to be defined. Furthermore, ameloblastoma in small biopsies may closely mimic other basaloid neoplasms including SMARCB1-deficient carcinomas which on occasion may display focal ameloblastoid pattern (13). Whether primary sinonasal ameloblastomas also harbor BRAF mutations similar to their gnathic counterparts, remains to be clarified in future studies (27).

NEUROENDOCRINE AND NEUROECTODERMAL NEOPLASMS

Esthesioneuroblastoma (ENBB; synonym: olfactory neuroblastoma)

This uncommon neoplasm is derived from the olfactory neuroepithelium with the majority of cases originating within the nasal cavity, mainly the superior nasal vault (1). The histology of ENB varies greatly both architecturally and cytologically and with regard to the degree of anaplasia as well (1). The significant variation from one tumor to another and within the same tumor underlines the wide differential diagnosis and the value of grading to predict prognosis and hence help selecting patients at increased risk of relapse for adjuvant treatment. Among the different grading schemes proposed, the 4-tiered HYAM grading system gained wider acceptance (1). The prototypical (low-grade) ENB recapitulates the pattern of well differentiated neuroblastic and paraganglionic neoplasms with prominent lobules and insular nests (Zellballen) of monomorphic medium-sized rounded cells having clear-cut neuroendocrine cytology and bordered by complete or discontinuous layer of slender S100-positive sustentacular cells. A variable neuropil-like matrix and ganglion cell-like differentiation is seen in many of the low-grade cases. On the contrary, high-grade tumors (grade 3 & 4) tend to show rather diffuse growth of non-descript small to medium cells with variable atypia, necrosis and brisk mitotic activity. Their lobular architecture varies greatly and is usually less prominent. In the opinion of the author, several neoplasms reported in older series as high-grade ENB (in particular those with prominent teratoma-like rosettes) might have represented other yet improperly classified poorly differentiated sinonasal epithelial neoplasms in the spectrum of high-grade non-intestinal-type adenocarcinoma and/or teratocarcinosarcoma (28-30) (Fig. 4). Low-grade ENB needs to be distinguished from typical and atypical carcinoid tumors while high-grade ENB needs to be distinguished from primary sinonasal and metastatic small (and large cell) neuroendocrine carcinoma (SCNEC) of pulmonary type (31). While presence of areas of conventional ENB and variation in the degree of atypia and growth pattern is frequently seen in ENB, this is usually not a feature of small cell carcinoma which essentially shows uniformly high-grade anaplastic cell features with extensive areas of necrosis, very high mitotic activity and solid growth throughout. On the other hand, a diffuse cytokeratin pattern supports diagnosis of SCNEC and argues against ENB (31). Recently, strong and diffuse expression of calretinin was proposed as a useful immunomarker for ENB (32).

Small cell neuroendocrine carcinoma (SCNEC), pulmonary type

This uncommon neoplasm in the sinonasal tract recapitulates features of SCNEC of pulmonary origin and of other organs and thus diagnosis needs to be complemented by staging imaging to exclude metastasis from pulmonary primary or from Merkel cell carcinoma. There are no histopathological features specific to the sinonasal tract. However, the presence of an exocrine (SCC, adenocarcinoma, etc.) component indicates a primary origin in the sinonasal cavities (33-35). While the expression of specific transcription factors (e.g. TTF1) might be indicative of a pulmonary origin of SCNEC, albeit not fully reliable, poorly differentiated NEC as a component of mixed adenoneuroendocrine carcinoma of the intestinal type may express CDX2 as an indication of origin from the intestinal type epithelial differentiation (34). Likewise, NEC originating from intestinal-type adenocarcinoma may retain CK20 expression and should be distinguished from Merkel cell carcinoma (different CK pattern). The most critical differential diagnosis of sinonasal SCNEC is solid-pattern alveolar rhabdomyosarcoma which is uniformly CD56 and ISL1 positive and may on occasion show epithelial (CK) and neuroendocrine (synaptophysin, chromogranin A) trait (36). Large cell NEC (LCNEC) of the head and neck is a poorly characterized neoplasm but it is essentially diagnosed by same criteria as its counterpart of pulmonary, GI tract and other organ origin. Sinonasal LCNEC is exceptionally rare and may be HPV-related (37).

Ewing family tumors and variants

Ewing family tumors (EFT) is exceedingly rare in the sinonasal tract but is supposed to be of better prognosis than conven-

tional skeletal and peripheral Ewing sarcomas. The conventional variant is essentially identical to its skeletal counterpart (Fig. 5). However, EFTs in the head and neck area may pose diagnostic confusion due to their known overlap with other undifferentiated small blue round cell neoplasms at this location, particularly in the sinonasal tract (38). Specifically, the Ewing sarcoma variant referred to as the adamantinoma-like variant is known for showing overt epithelial (squamous) differentiation associated with diffuse cytokeratin expression. Two of 7 recently reported cases originated in the sinonasal tract and most were initially misclassified as carcinomas (39). Younger mean age (31 years) may be a helpful initial clue to alert to this possibility. Histologically, adamantinoma-like EFTs are almost indistinguishable from basaloid carcinomas and this is further complicated by strong diffuse expression of pancytokeratin and p40. In addition, variable expression of p16, protein S100 and synaptophysin in some cases further contributes to this confusion. In the experience of the author (unpublished data), CD99 immunostaining, if positive, is not reliable in excluding basaloid carcinomas. Furthermore, detection of the EWSR1 gene fusion by FISH, while helpful to exclude basaloid SCC, it is not useful in ruling out other possibilities such as myoepithelial carcinoma (40), thus it seems advisable to use RT-PCR or other methods to define both gene fusion partners for exact classification of EFT at this site.

Small cell amelanotic melanoma

Sinonasal malignant melanomas are only rarely highly pleomorphic. Instead, they tend to display either monotonous small round cell morphology, with or without pigmentation, or a compact fibrosarcoma-like spindle cell pattern. In both instances aberrant expression of epithelial (pancytokeratins) and neuroendocrine markers is not uncommon and might be the source of misclassification if melanoma is not considered and thus melanocytic markers not included in the immunopanel used. The main differential diagnosis in this setting is SCNEC (and large cell variant) and Ewing sarcoma (Fig. 5). Thus inclusion of protein S100 and melanoma cocktail or HMB45 is mandatory. Fortunately the majority of small cell sinonasal melanomas (in the author´s experience) retain a strong expression of almost all melanocytic markers. If aberrant cytokeratin is suspected, lack of high molecular weight cytokeratins and of specialized cytokeratin (CK7 and CK19) are potential indicators of a non-epithelial origin. The clinical history might on occasion be the only clue for diagnosis of dedifferentiated small cell melanoma with aberrant expression of cytokeratins and/or neuroendocrine markers and in such cases genotyping of BRAF/NRAS would be of help in the appropriate context (41).

Neoplasms with overlapping features of more than one lineage and neoplasms with aberrant phenotypes: diagnostic pitfalls

As pointed out in the introduction, a feature special to the sinonasal cavities is the occurrence of neoplasms of different histogenetic derivation but with significantly overlapping clinicopathological, morphological and immunophenotypic features (28-30). This enhances the probability of misinterpreting one entity as another with serious prognostic and therapeutic implications, particularly in small biopsies. Taken together, poorly differentiated sinonasal tract neoplasms tend to show:

- non-descript small round cell or basaloid "blue cell" morphology in a desmoplastic or fibrotic background (37),
- occasional reactivity for cytokeratins, albeit some of them being non-epithelial in origin,
- frequent expression of neuroendocrine markers, albeit highly variable in intensity and extent,
- common reactivity for CD56 which may indicate either T-cytotoxic cell, myeloid cell, myeloma cell, rhabdomyogenic cell, neuroendocrine cell or nonspecific trait,
- expression of protein S100 that might point to myoepithelial, melanocytic or biphenotypic mesenchymal differentiation, and
- more than one line of differentiation as seen in teratocarcinosarcoma and ENB with rhabdomyoblastic differentiation (42).

Thus a sinonasal small round cell neoplasm coexpressing cytokeratin in variable extent with diffuse expression of synaptophysin and CD56 might well be either a SCNEC or solid-pattern alveolar rhabdomyosarcoma. Likewise, membranous expression of CD99 is a frequent feature in poorly differentiated carcinomas as well as in small cell melanoma and might be mistaken for Ewing sarcoma family tumor. Accordingly, a high suspicion index and appropriate use of well selected supplementary immunohistochemistry panel and molecular testing are mandatory for correct classification of poorly differentiated sinonasal malignancies. At the end, several malignant sinonasal neoplasms remain currently unclassifiable (Fig. 6), until defined criteria have been established.

CONFLICT OF INTEREST

The author declare that there is no conflict of interest regarding the publication of this paper.

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