Sinonasal tumor pathology: what’s new?

A. FRANCHI
Department of Surgery and Translational Medicine, Section of Anatomic Pathology, University of Florence, Italy

Key words
Nasal cavity • Paranasal sinuses • Tumor • Histopathology • Genetic changes

Summary
The sinonasal tract is an anatomical region affected by a wide variety of tumors with different clinical behavior, histologic and molecular features. Substantial advances have been made in the field of sinonasal tumor pathology in recent years, including improvement in the diagnosis, treatment and genetic characterization. In this article, a review of the histological features of new distinctive pathologic entities as well as newly described molecular alterations of these rare tumors is presented.

Introduction
The sinonasal tract is an anatomical region affected by a wide variety of tumors arising from the surface and glandular epithelia, as well as from the supporting structures. These are rare tumors with an annual incidence of approximately 1 case per 100,000 inhabitants worldwide. Overall, squamous cell carcinoma and adenocarcinomas account for over 80% of all sinonasal malignancies. Exposure to wood dust, leather dust and other chemical agents are well known aetiological factor for the intestinal type adenocarcinoma, while for other tumor types the risk factors are not well understood. Their development therefore most likely occurs according to different molecular pathways, which to date have been only partially investigated. Substantial advances have been made in the field of sinonasal tumor pathology in recent years, including improvement in the diagnosis, treatment and genetic characterization. In this article, a brief review of the new distinctive pathologic entities and molecular features of these rare tumors is presented.

Recently described sinonasal malignancies

NUT carcinoma
NUT carcinoma (NC) is a highly aggressive carcinoma defined by a reciprocal chromosomal translocation, which in most cases involves the NUT (nuclear protein in testis) gene on chromosome 15q14.6 and the BRD4 (bromodomain-containing protein 4) gene on 19p13.1. In the sinonasal tract NC represents approximately 2% of all carcinomas, and occurs at all ages with a predilection for young adults. Histologically, it is a high grade poorly differentiated carcinoma, consisting of nests and sheets of monotonous round cells, but foci of mature keratinized squamous cells may be occasionally seen abruptly juxtaposed to the undifferentiated component (Fig. 1). brisk mitotic activity, apoptotic bodies, and areas of necrosis are often recognized. The diagnosis requires the identification of NUT rearrangement, by FISH or RT-PCR, but immunohistochemical staining for NUT is sensitive and specific in the distinction of NC from other carcinomas. In addition, NC is positive for cytokeratins, p63, 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, alphafetoprotein, neuron specific enolase, CD57, and CD99. HPV and EBV have been negative in all cases tested.

HPV-related carcinoma with adenoid cystic-like features
This recently described tumor type presents significant overlap with adenoid cystic carcinoma, particularly with the solid variant. It consists of solid nests of basoaloid cells with areas showing cribriform architecture with accumulation of extracellular mucoid material (Fig. 2).
The overlying epithelium often shows areas of dysplasia. Necrosis and brisk mitotic activity are usually present. Immunohistochemical studies reveal two cell populations, myoepithelial cells positive for S100, actin, p63 and calponin, and duct-like cells positive for c-kit. Both the dysplastic surface epithelium and the tumor cells are positive for p16, and high risk HPV can be demonstrated by in situ hybridization. Subtyping of HPV reveals more frequently the rare type 33. The main differential diagnosis is with adenoid cystic carcinoma. The presence of surface intraepithelial dysplasia, absence of MYB gene rearrangement and association with HPV allows a separation of the two entities. Distinction from basaloid squamous carcinoma is based on the presence of myoepithelial cells. Although the number of cases reported so far is small, the clinical behavior of this tumor type seems to be relatively indolent, making its distinction from other high-grade sinonasal carcinomas likely to be clinically relevant.

SMARCB1 (INI-1) Deficient Sinonasal Carcinoma

This is a high-grade clinically aggressive carcinoma, usually presenting in advanced stage, with invasion of bone structures. Histologically, the hallmark is the presence of a variable number of rhabdoid or plasmacytoid tumor cells, with abundant, eccentric, eosinophilic cytoplasm, within a neoplastic population of basaloid appearing cells. Squamous or glandular differentiation is not evident as it is dysplasia or carcinoma in situ of the surface epithelium.

All cases are diffusely positive for cytokeratins and negative for INI1. Other markers, including p63, p40 and synaptophysin have been variably positive. P16 was positive in a subset of cases, but HPV has not been demonstrated. The mechanisms responsible for loss of INI expression were homozygous or heterozygous deletion of SMARCB1 in most cases. SMARCB1 (INI-1) deficient sinonasal carcinoma should be distinguished...
from other high-grade sinonasal carcinomas, including sinonasal undifferentiated carcinoma (SNUC), basa-
loid squamous cell carcinoma and NUT carcinoma. The
identification of rhabdoid cells and negative immunos-
taining for SMARCB1 (INI-1) help in the distinction.

**Biphenotypic sinonasal sarcoma**

Biphenotypic sinonasal sarcoma is a recently recog-
nized entity 7, which is characterized by rearrangements
of \(PAX3\), most frequently translocated with \(MAML3\) 8. Huang et al. recently reported a subset of tumors harbor-
ning the same \(PAX3\)-NCOA1 fusion that can be seen in
alveolar rhabdomyosarcoma 9. It typically involves the
nasal cavities and ethmoid sinuses, with predominance
in adult women. The clinical behavior is indolent, with
possible local recurrence, but neither distant metastases
nor death for disease have been reported so far.

Histologically, it is a fasciculated proliferation of uni-
form spindle cells, which infiltrates the mucosa and the
bone (Fig. 3). It is often accompanied by prominent
“staghorn” vessels and hyperplastic epithelial elements
entrapped within the tumor. Immunohistochemically,
neoplastic cells are positive for smooth muscle actin,
calponin, and S100, while desmin, EMA, and cytokera-
tins are only occasionally detectable. Tumors with the
\(PAX3\)-NCOA1 fusion present focal rhabdomyoblastic
differentiation, consisting in the presence of rare strap
cells and myogenin immunoreactivity. The main differ-
ential diagnosis is with cellular schwannoma and mali-
gnant peripheral nerve sheath tumor (MPNST). Schwan-
nomas are diffusely and strongly positive for S100 pro-
tein, while in BSS S100 positivity is not diffuse; more-
over SOX10 is negative in BSS while schwannoma is
negative for actins. MPNST has usually a high-grade
appearance and it is more cellular and atypical than
BSS. Other sinonasal spindle cell tumors to be ruled out
are glomangiopericytoma, which is S100 negative, and
solitary fibrous tumor, which is also negative for S100
and presents STAT6 positivity. In case, the demonstra-
tion of \(PAX3\) rearrangements rules out other diagnostic
considerations.

**Sinonasal renal cell-like adenocarcinoma**

This recently described primary sinonasal tumor is a
close mimicker of metastatic clear cell carcinoma of the
kidney 10-12. It is composed of a proliferation of clear cu-
boidal or columnar cells forming gland-like structures,
follies or solid nests, often with an hemorrhagic back-
ground. The distinction from metastatic clear cell renal
cell carcinoma is based on the negativity for \(PAX8\),
renal cell carcinoma antigen (RCC) and vimentin. Sal-
ivary gland-type tumors, including hyalinizing clear cell
carcinoma, mucoepidermoid carcinoma, and myoepithelial
carcinoma may show clear cell areas and may be en-
tered in the differential diagnosis. Although designated
as adenocarcinoma, none of the patients reported so far
have experienced recurrence or metastatic disease.

**Recent advances in the molecular genetics of sinonasal epithelial tumors**

**Human papilloma virus in sinonasal carcinomas**

It is now well established that high risk human papillo-
ma virus (HPV) is an etiologic factor of head and neck
squamous cell carcinomas, particularly of those arising
in the oropharynx. A number of studies have also iden-
tified high risk HPV in sinonasal carcinomas, but with
highly variable detection rates, and this may reflect the
different type of assays used and the histologic subtypes
included 13-17. Overall, the rate of high-risk HPV detec-
tion ranges between 15 and 20%, with a higher preva-
ience in certain histotypes, including non-keratinizing
squamous cell carcinoma, basaloid squamous cell car-
cinoma, papillary squamous cell carcinoma and aden-
osquamous carcinoma, while conventional keratinizing
squamous cell carcinoma is less frequently positive 18.
Thus, while high risk HPV appears to be implicated in the development of a subset of sinonasal carcinomas, it is still controversial whether this has an impact on prognosis 14 16 17.

**Distinctive molecular alterations in sinonasal epithelial tumors**

Sinonasal papillomas (SP) or Schneiderian papillomas are rare benign neoplasms that can be histologically distinguished in three groups, exophytic, inverted, and cylindrical or oncocytic. It is well known that the sinonasal papilloma types differ for their incidence, involved anatomic site, and clinical behavior, including the frequency of local recurrence and malignant transformation. Recent studies have suggested that sinonasal papillomas may develop along different molecular pathways. Indeed, activating EGFR mutations have been identified in 88% of inverted sinonasal papillomas and 77% of carcinomas arising in inverted papillomas 19. Moreover, the same EGFR mutations were identified in inverted papillomas and synchronous or metachronous carcinomas, supporting a role of inverted papillomas as a precursor lesion for sinonasal squamous carcinomas. These EGFR mutations appear to be specific for inverted papillomas and sinonasal carcinomas arising in inverted papillomas, as they were not found in other papilloma types and sinonasal carcinomas not arising in papillomas 19.

On the other hand, sinonasal oncocytic papillomas presented KRAS mutations in 100% of the cases, and an identical mutation was detected in sinonasal carcinomas arising in oncocytic papillomas 20. Again this molecular alteration appears to be specific for this subset of papillomas, as it was not detected in other sinonasal epithelial neoplasms 20. Overall, these results suggest that sinonasal papillomas may develop along different molecular pathways: inverted papillomas present EGFR mutations, while oncocytic papillomas are characterized by KRAS mutations, and exophytic papillomas are associated with low-risk HPV infection. Although the reason for this genotype-phenotype correlation is not clear, the histologic differences between sinonasal papillomas may reflect a difference in the cell of origin and the presence of other currently unknown mutations. Nevertheless, the identification of these mutations opens the possibility of new targeted treatments in these tumors 21.

The status of the EGFR-RAS-RAF-signaling cascade has also been investigated in sinonasal carcinomas. EGFR amplification and/or overexpression have been detected in a subset of intestinal type adenocarcinomas, with frequency ranging between 10 and 40%. EGFR gene copy number gains have been detected in up to 50% of the cases, but EGFR protein overexpression was found in a lower number of cases 22. In addition, activating mutations of EGFR gene have not been identified in these tumors 23. KRAS has been so far the most studied oncogene in sinonasal carcinomas. Mutations have been detected with variable, generally low frequency, being more common in adenocarcinomas (0-30% of cases) than in squamous cell carcinomas (1% of cases) 24-28. Interestingly, KRAS mutations consisted prevalently of G → A transitions, a type of mutation typically produced by alkylating agents in experimental systems, and this could be related to a combination of exposure to tobacco, wood dust, and possibly other occupational agents 28. KRAS mutations tend to occur more frequently in intestinal type adenocarcinomas arising in woodworkers, and a correlation has been observed with histologically less aggressive subtypes 23 28. Moreover, in a recent study, patients affected by intestinal type adenocarcinoma with KRAS mutations had significantly improved clinical behavior 27. Other genes of the RAS family, have only sporadically been investigated, and only one adenocarcinoma with HRAS mutation was identified in two studies 15 28.

In conclusion, in recent years a number of studies have started to define the molecular landscape of sinonasal tumors and hopefully this will soon open to the possibility of testing new drugs for improving the treatment and outcome of these rare neoplasms.

**References**

13. El-Mofty SK, Lu DW. Prevalence of high-risk human papillomavirus DNA in nonkeratinizing (cylindrical cell) carcinoma of the
SINONASAL TUMOR PATHOLOGY: WHAT’S NEW?

13


