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Review - Study Group GIPaTeC

Sinonasal tumor pathology: what's new?

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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 [1]. In the sinonasal tract NC represents approximately 2% of all carcinomas [2], 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 [3]. 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 basaloid cells with areas showing cribriform architecture with accumulation of extracellular mucoid material (Fig. 2).

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Fig. 1. NUT carcinoma. Abrupt keratinization (arrow) is visible in this otherwise undifferentiated carcinoma (A). The tumor showed nuclear positivity for NUT (B).

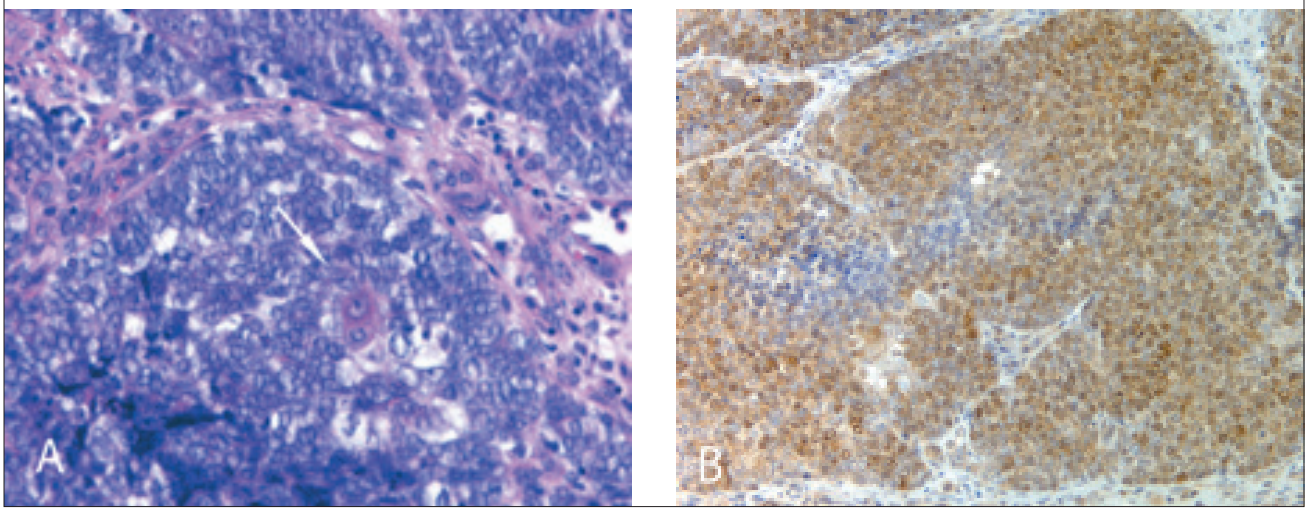
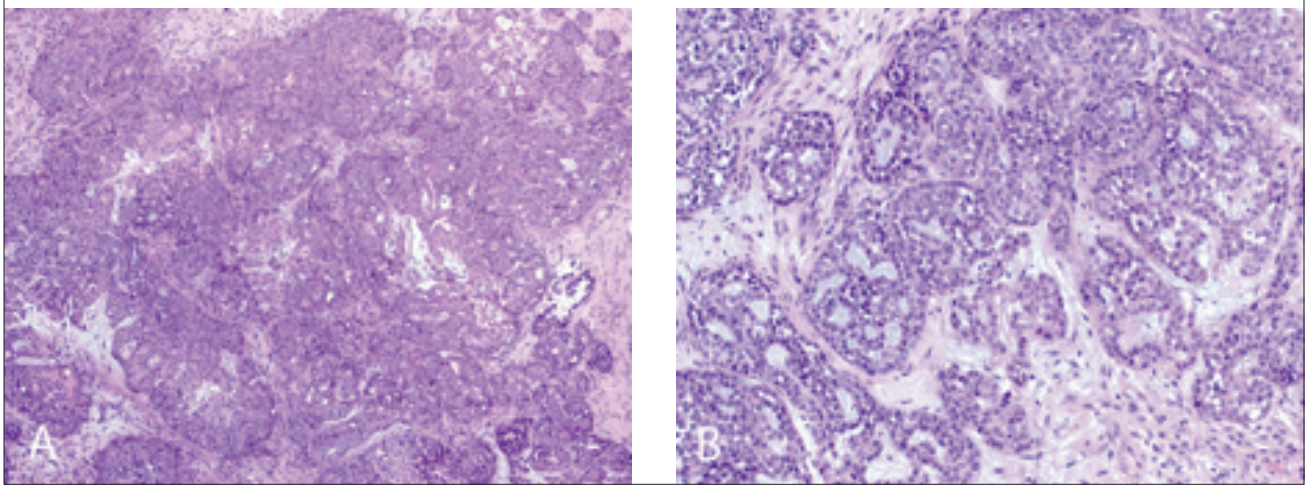


Fig. 2. HPV-related carcinoma with adenoid cystic-like features. The tumor is composed of a uniform population of basaloid cells with nested architecture (A). Cribriform areas (B).



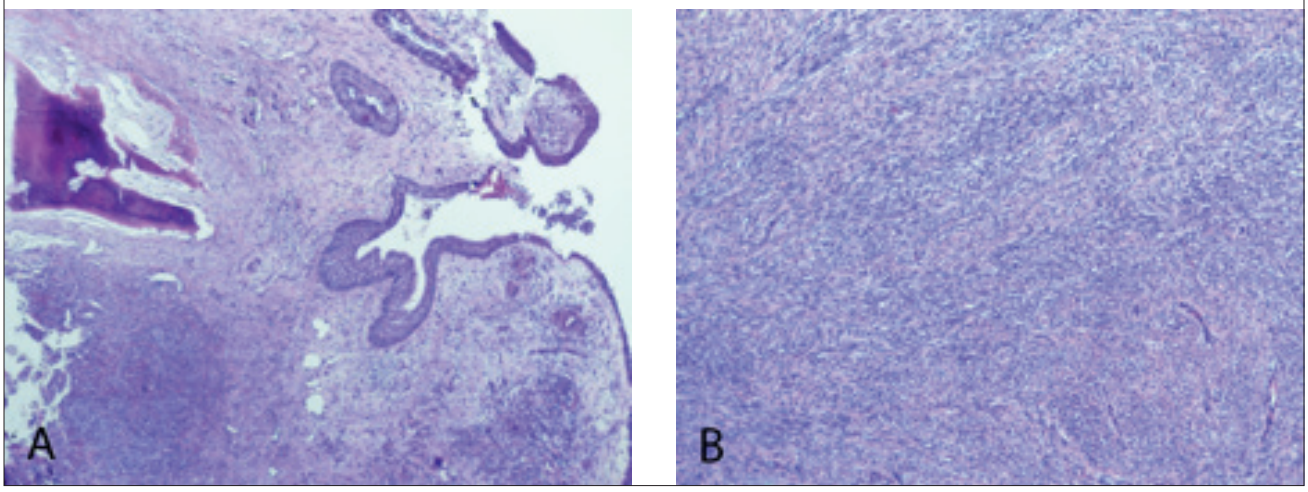
The overlying epithelium often shows areas of dysplasia. Necrosis and brisk mitotic activity are usually present. Immunohistochemical studies reveal two cell populations, myoepithelial cells positive for S100, actin, p63 and calponin, and duct-like cells positive for c-kit. Both the dysplastic surface 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 [4]. 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 [5 6].

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

Fig. 3. Biphenotypic sinonasal sarcoma. The nasal mucosa and bone are infiltrated by a spindle cell fascicular tumor (A). The spindle cells are arranged in fascicles with "herringbone" pattern (B).



from other high-grade sinonasal carcinomas, including sinonasal undifferentiated carcinoma (SNUC), basaloid squamous cell carcinoma and NUT carcinoma. The identification of rhabdoid cells and negative immunostaining for SMARCB1 (INI-1) help in the distinction.

Biphenotypic sinonasal sarcoma

Biphenotypic sinonasal sarcoma is a recently recognized entity [7], which is characterized by rearrangements of *PAX3*, most frequently translocated with *MAML3* [8]. Huang et al. recently reported a subset of tumors harboring 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 uniform 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 cytokeratins 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 differential diagnosis is with cellular schwannoma and malignant peripheral nerve sheath tumor (MPNST). Schwannomas are diffusely and strongly positive for S100 protein, while in BSS S100 positivity is not diffuse; moreover 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 demonstration 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 cuboidal or columnar cells forming gland-like structures, follicles or solid nests, often with an hemorragic background. The distinction from metastatic clear cell renal cell carcinoma is based on the negativity for PAX8, renal cell carcinoma antigen (RCC) and vimentin. Salivary gland-type tumors, including hyalinizing clear cell carcinoma, mucoepidermoid carcinoma, and myoepithelial carcinoma may show clear cell areas and may be entered 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 papilloma virus (HPV) is an etiological factor of head and neck squamous cell carcinomas, particularly of those arising in the oropharynx. A number of studies have also identified 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 detection ranges between 15 and 20%, with a higher prevalence in certain histotypes, including non-keratinizing squamous cell carcinoma, basaloid squamous cell carcinoma, papillary squamous cell carcinoma and adenosquamous 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 (0-50% 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.

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