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REVIEW ARTICLE

Sinonasal tumors: a clinicopathologic update of selected tumors

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Abstract The sinonasal cavities show a wide variety of neoplasms of epithelial, mesenchymal, neural/neuroectodermal or hematopoietic origin. The differential diagnosis for these tumors may be difficult due to overlapping morphologies, variable patterns in ancillary studies, and potentially confusing terminology. In this report, an updated review of the spectrum of neoplasia is provided, using the World Health Organization 2005 classification as a guide. Classic tumors that are generally limited to the sinonasal tract are described and new information regarding molecular pathogenesis is reviewed. Also new entities that have the sinonasal tract as a site of predilection, such as sinonasal renal cell-like adenocarcinoma and *NUT* midline carcinoma are highlighted.

Keywords Sinonasal tumors · Pathology · Immunohistochemistry · Molecular analysis · Treatment · Prognosis

Introduction

Surgical pathology of the sinonasal tract presents considerable diagnostic difficulties for the pathologist for several reasons. First, the anatomy of this region is very complex and while processing specimens care should be paid to ensure/preserve relationships between structures. Coupled with this, many of the unique lesions that occur in the sinonasal tract have a predilection for specific sites. Since the anatomic sites are often difficult to reach by standard biopsy approaches, specimens may be compromised in terms of integrity (fragmentation, cauterization artifacts,

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and degradation) and anatomical landmarks may be absent. Secondly, the tumors that arise in these locations may show overlapping histologic features, despite divergent pathogenesis and/or tissues of origin. Since treatment schemes are different for particular tumor types, it is important for the pathologist to sort out the differential diagnosis. Ancillary investigations may also show overlapping and/or aberrant findings, which may increase difficulties in histologic diagnosis/classification. Finally, the pertinent literature may be confusing with regard to terminology and traditional classifications have been modified on the basis of immunohistochemical and molecular findings. In this review a wide variety of lesions will be examined with emphasis on current understanding of histologic patterns, ancillary testing and clinical findings. For the discussion, the lesions are grouped into those derived from the mucosal surface and those that originate from other tissue types.

Tumors of the mucosal surface

Schneiderian papillomas

Schneiderian papillomas are epithelial tumors that arise from the respiratory mucosa (Schneiderian membrane) that lines the nasal cavity and the paranasal sinuses. Three histological subtypes are recognized: inverted papilloma, oncocytic papilloma and exophytic papilloma [1].

Inverted papilloma

This is the most common variant. It shows a male predilection and usually occurs in individuals above 40 years of age. The tumor typically arises from the lateral nasal wall and often extends into one or more adjacent sinuses. The nasal septum is involved (usually secondarily) in approximately 5 % of cases.

Histologically, inverted papillomas show endophytic growth, though often contain an exophytic or polypoid component as well. The lesion is characterized by proliferative epithelium invaginating into edematous stroma (Fig. 1). The epithelium is multilayered, often more than ten layers thick. The invaginations into the underlying stroma show medium to large sized nests of cells that typically have a rounded, smooth border. The epithelial phenotypes may vary, but they are usually transitional (occasionally referred to as cylindrical). Squamous areas, ciliated cells on surface, dispersed mucous cells and superficial keratinization can be seen. Within the epithelium, there are also small cystic spaces that contain cell debris and inflammatory cells. Although there is no significant stromal reaction, neutrophils transmigrating through the epithelium are usually seen. This is a useful diagnostic feature.

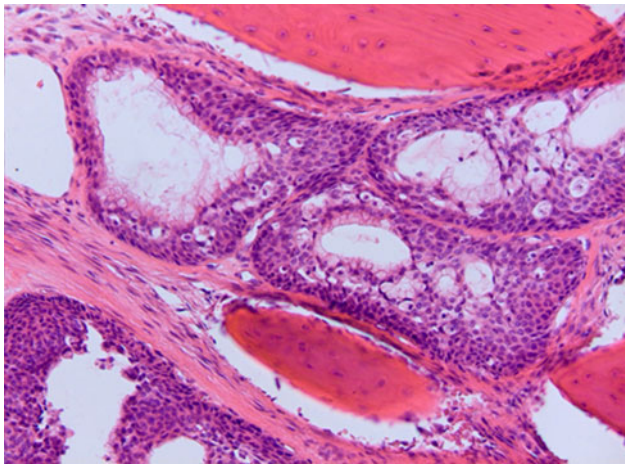

Fig. 1 Inverted papilloma. In spite of its monotonous histologic appearance, the lesion erodes the bony sinus walls

Inverted papillomas can show areas of cellular/nuclear atypia and increased mitotic activity. If the atypia is extensive, the possibility of malignant transformation should be considered. Whether the presence of mild or very focal atypia *ipso facto* has any clinical or prognostic significance is controversial [2] and minimum criteria for a diagnosis of frank dysplasia in inverted papilloma have not been established.

Inverted papilloma can be seen in association with squamous cell carcinoma (SCC) in about 11 % [3, 4]. If atypia is extensive, and combined with necrosis and destructive growth, the possibility of a malignant component rather than inverted papilloma should be considered. Two diagnostic possibilities are generally considered in these cases: malignant transformation of an inverted papilloma (carcinoma *ex* Schneiderian papilloma) or co-existence of pathogenetically unrelated benign and malignant lesions. Histologically, gradual transition from a typical inverted papilloma through dysplastic alterations to frankly invasive SCC suggests malignant transformation. When such a transition is not seen and the histology is characterized by two sharply demarcated components, co-existence of inverted papilloma and independently arising SCC can be considered. There are no definitive markers indicative of malignant transformation, but some studies suggest that increased, immunohistochemically assessed, proliferation indices and/or the expression of p53 would be of help [5–7].

The prognosis in inverted papillomas is good provided they are adequately treated, which usually means complete removal of tumor and surrounding sinonasal mucosa at the involved site. In incompletely excised/neglected cases, intracranial extension and death may occur. For lesions associated with SCC, radiotherapy adjuvant to surgical excision is recommended [8].

The etiology of inverted papilloma is not completely understood and the molecular events that lead to its evolution are not well studied. More extensively investigated, is the relationship between inverted papilloma and human papilloma virus (HPV). Unfortunately, the data on this relationship are controversial and whether HPV is causative or a bystander is debatable [9]. However, most studies using sophisticated and sensitive technologies, have identified up to 30 % of inverted papillomas as positive for HPV [10]. Interestingly, at least one study also examined $p16^{ink4a}$ in the same cases, and found that expression was nearly ubiquitous, regardless of HPV status, implying that p16 cannot be used as a surrogate marker in these cases, as it is in HPV-associated SCC of other mucosal sites [11].

Oncocytic papilloma

This lesion is also known as cylindrical cell papilloma or columnar cell papilloma. It can occur at the same sites and with the same age distribution as inverted papilloma. In contrast with inverted papilloma, however, oncocytic papilloma does not show any gender predilection [1, 12, 13].

Histologically, oncocytic papilloma may show invaginated, exophytic or polypoid appearances. It is composed of multilayered, cylindrical epithelial cells with the appearance of oncocytes. At the surface layer, some cells may show cilia. Similarly to inverted papilloma, intraepithelial microcysts with mucus and/or cell debris may be present (Fig. 2). These cysts are entirely limited to the epithelium and do not involve the underlying stroma.

Histologically oncocytic papilloma may be confused with low-grade papillary adenocarcinoma. However, lack of invasive growth, epithelial stratification and presence of intraepithelial cysts are distinguishing features. Distinction from inverted papilloma should be based on the easily recognized oncocytic phenotype and exophytic growth. "Hybrid'' oncocytic/inverted papillomas may be seen. This in conjunction with the various similarities may tempt the pathologist to adopt a "lumper'' rather than "splitter'' attitude while reporting on sinonasal papillomas. It may be prudent, however, to distinguish these various subtypes, as not yet further substantiated preliminary data suggest that oncocytic papilloma may show a higher rate of recurrence/malignant transformation [13]. Importantly, the same treatment principles apply for oncocytic papillomas as for inverted papilloma [13].

Exophytic papilloma

Exophytic papilloma (everted papilloma or fungiform papilloma) is mainly seen in men and occurs at a younger age than inverted/oncocytic papilloma [1, 12]. Exophytic papillomas are usually seen in the vicinity of the lower nasal septum and only rarely occur on the lateral nasal wall where inverted/oncocytic papillomas typically originate.

Histologically, exophytic papillomas are composed of papillae lined with multilayered epithelium that may vary from squamous to columnar with scattered mucous cells (Fig. 3). Surface keratinization is secondary and a reactive response. When secondary keratinization is extensive, the lesion must be distinguished from verruca vulgaris that may be seen in the skin lining the nasal vestibule. Hyperkeratosis/granulosis (prominent granular layer) and stromal vascularity characterize verruca vulgaris and may be useful in diagnosis. Treatment is more limited than for the other types of Schneiderian papillomas which generally require more extensive procedures compared to a simple excision for the exophytic papilloma.

Squamous cell carcinoma

Squamous cell carcinoma is the most common malignancy arising from the mucosal surfaces that line the upper

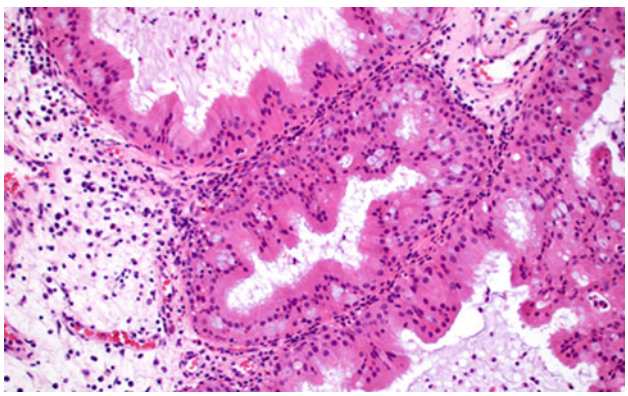

Fig. 2 Oncocytic papilloma. Classical appearance of a lining composed of oncocytic columnar cells and containing tiny cysts

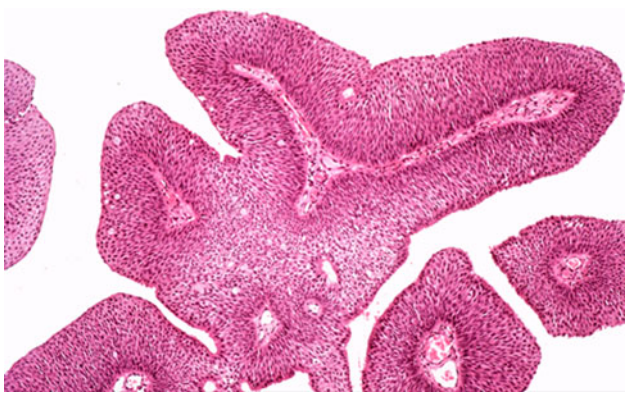

Fig. 3 Exophytic papilloma covered with an epithelial lining composed of columnar cells. There is no keratinization

aerodigestive tract. In the sinonasal tract, both keratinizing and non-keratinizing SCC occur. Other histological subtypes that are typically found elsewhere in head and neck (e.g. verrucous, basaloid, spindle cell carcinoma) are much rarer in the sinonasal cavities.

Non-keratinizing SCC has variously been referred to as cylindrical cell carcinoma (Ringertz' carcinoma), transitional cell carcinoma, and Schneiderian carcinoma [14]. This type accounts for 9.5 % of all sinonasal malignancies [15]. Reference to it can be found as early as 1900. As inferred by the multiple terms, classification has been controversial; we advocate the use of the WHO nomenclature that recognizes cylindrical cell carcinoma as one of the synonyms of sinonasal non-keratinizing SCC [14].

The tumor was described by Ringertz in 1938 [16], and those original descriptions have largely held up. It can be papillary, but is basically a non-keratinizing epithelial tumor that invaginates into the underlying stroma. There is a sharp demarcation at the epithelium-stroma interface, giving rise to an overall appearance simulating ribbon or garland-like patterns with central necrotic areas. The tumor consists of rather uniform non-keratinizing cells with only occasional pleomorphism, that are mainly cylindrical and often arranged perpendicularly to the tumor-stroma interface. There can be distinctive peripheral palisading. The advancing front may be pushing, which makes difficult assessment of invasion, particularly when small biopsy specimens are examined (Fig. 4).

Sinonasal SCCs of both the keratinizing and non-keratinizing types account for approximately 50 % of all mucosal malignancies of the sinonasal tract [17]. Clinical symptoms are usually non-specific and include unilateral nasal obstruction and epistaxis. An ulcerated intraoral palatal mass appears when a maxillary sinus tumor invades palatal bone.

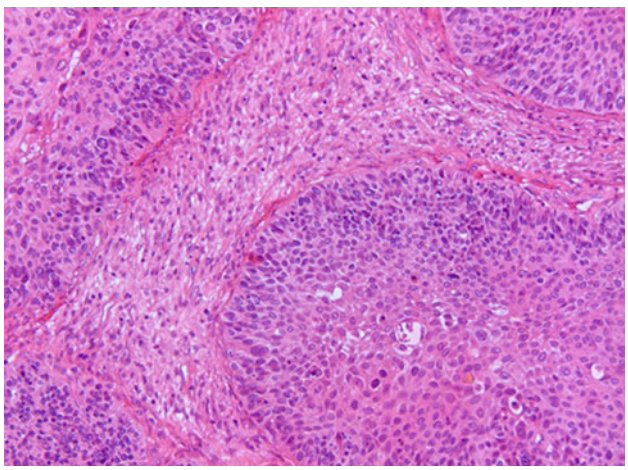

Fig. 4 Tumor-stroma interface in non-keratinizing squamous cell carcinoma. Note the sharp demarcation

In spite of substantial improvements in surgical techniques and radiotherapy, prognosis of sinonasal SCC is still poor with a 50 % 5-year survival [17]. However, these low figures date from a period in which no distinction was made between non-keratinizing carcinoma and conventional SCC whereas recently, evidence has accumulated that non-keratinizing carcinoma should be considered as a distinct histopathologic and molecular disease entity with suggested etiologic relationship to high risk HPV [18] and with a more favorable prognosis [19]. So the survival figure mentioned above may be too ominous for this latter tumor which suggests that the outcome for conventional sinonasal SCC of the keratinizing type may be even worse.

The issue of an etiological relationship between non-keratinizing carcinoma and inverted Schneiderian papilloma has been discussed above [2].

Sinonasal undifferentiated carcinoma

Sinonasal undifferentiated carcinoma (SNUC) is a rare, aggressive lesion with a broad age range and predilection for males [20]. At the time of diagnosis the tumor is rarely limited to a single sinus but typically involves multiple adjacent areas.

Histologically, the tumor is composed of cells without obvious squamous or glandular differentiation. The cells show medium-sized to large nuclei and nucleoli that may be either single, prominent or multiple. The cells are arranged in nests, lobules, trabeculae or sheets. There is usually extensive necrosis and a lack of prominent inflammatory or desmoplastic reaction. Immunohistochemistry shows positivity for pan-cytokeratins and simple keratins [20–22] and is valuable in differentiating SNUC from sinonasal tumors composed of poorly differentiated small cells (Fig. 5). The differential diagnosis is broad, and includes neuroendocrine carcinoma, olfactory neuroblastoma, embryonal type rhabdomyosarcoma, lymphoma and melanoma. Moreover, SNUC should be distinguished from the newly described primary sinonasal "nasopharyngeal-type undifferentiated carcinoma" (NPTC), since NPTC has a better prognosis and is more responsive to radiotherapy than SNUC; demonstration of EBV by EBV encoded RNA (EBER) in situ hybridization is seen in NPTC, but not in SNUC [22]. The prognosis of SNUC is poor with a 5-year survival of approximately 35–50 % [17, 23]. Combined surgery and adjuvant radiotherapy likely offer the best chance of cure compared with either modality alone. The impact of adjuvant chemotherapy is unclear [23]. Induction chemotherapy followed by concurrent chemoradiation is a promising new treatment strategy in this rare tumor type [24].

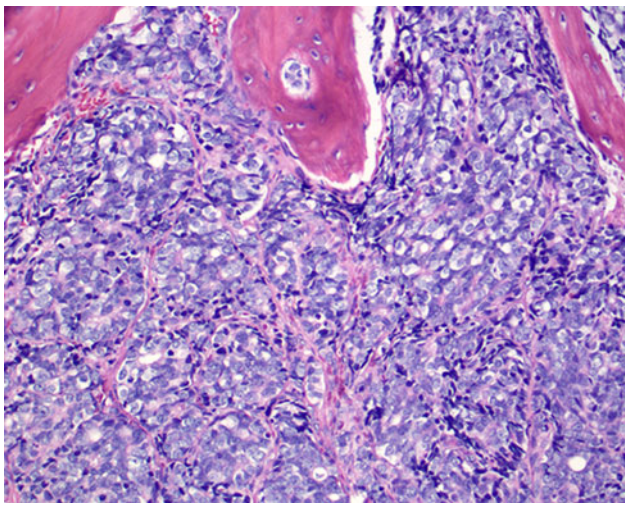

Fig. 5 Sinonasal undifferentiated carcinoma; closely packed cells lacking any differentiation invade between bony trabeculae

NUT midline carcinoma

This very rare tumor was originally described in children and young adults as a highly aggressive and often lethal tumor of midline sites. The tumor is uniquely characterized by chromosomal rearrangements of the gene encoding nuclear protein of the testis (*NUT*), located at 15q14. Relatively few cases have been reported [25, 26] with six involving the sinonasal tract. There is no gender predilection, with a wide age range at presentation.

Histologically, *NUT* midline carcinomas show sheets of undifferentiated cells, with areas of abrupt squamous differentiation (Fig. 6). Strong CD34 immunoreactivity is often seen. The differential diagnosis includes other undifferentiated high-grade malignancies: small blue round cell tumors (such as Ewing sarcoma/primitive neuroectodermal tumor (PNET), rhabdomyosarcoma, desmoplastic small round cell tumor), melanoma, olfactory

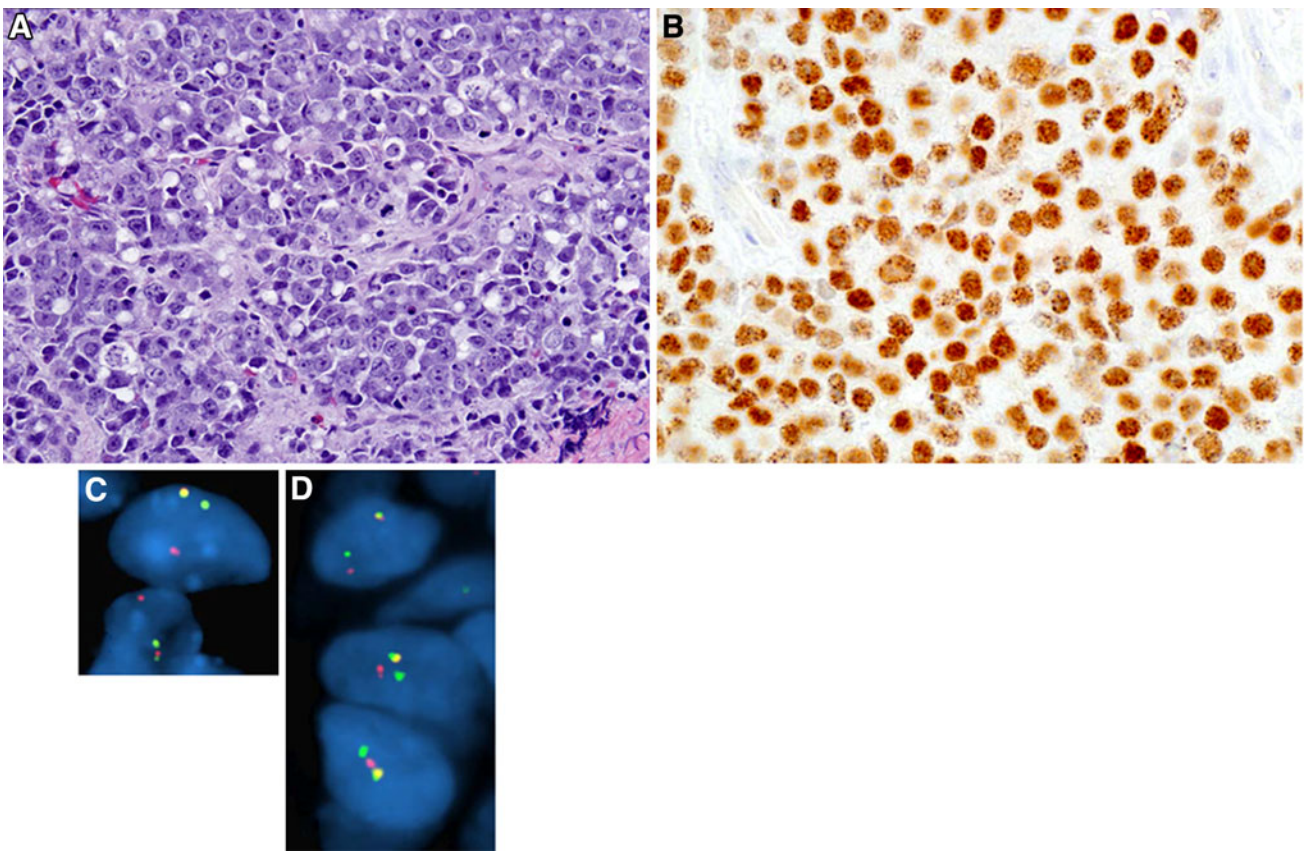

Fig. 6 *NUT* midline Ca. Poorly differentiated carcinoma (**A**) exhibiting nuclear expression of *NUT*-antibody (**B**). FISH evaluation for *BRD4-NUT* rearrangement was performed with a Homebrew *BRD4-NUT* dual color, dual fusion translocation probe for *NUT/C15ORF55* at 15q14 (**C**) and *BRD4* at 19p13.12 (**D**). The result is interpreted as abnormal. Rearrangement was observed in 47 of 50 nuclei (normal range up to 1 % fusions). Pictures courtesy of Dr. K. Star and Dr. CA French, Brigham and Women's Hospital, Boston, USA

neuroblastoma, high-grade hematologic malignancies and undifferentiated carcinomas. Although immunohistochemistry may be helpful in either identifying or excluding some of these possibilities [27], the definite diagnosis of *NUT* midline carcinoma depends upon the demonstration of the specific translocation by FISH or PCR techniques [26].

Survival rate is poor. Currently, there is no standard treatment for *NUT* midline carcinoma: patients are usually treated with platinum-based or lymphoma-type multi-drug chemotherapy regimens and radiotherapy, with subsequent resection performed only occasionally. In spite of aggressive treatment, the average survival time is 9–10 months, although targeted therapies show some promise [26].

Adenocarcinoma

Three main types of adenocarcinoma can be encountered in the sinonasal tract, with the most frequent category being salivary-type adenocarcinoma. This category will not be discussed, since these tumors generally tend to be typical salivary-type tumors, presumably arising from the seromucinous glands of the sinonasal tract. The other two categories are unique to this site and will be discussed here. These are intestinal-type adenocarcinoma (ITAC) and non-ITAC. A new tumor has also been recently described under the term renal cell-like adenocarcinoma; this will also be considered.

Intestinal-type adenocarcinoma

Intestinal-type adenocarcinoma is characterized by its very strong resemblance to carcinoma of the colon. Its frequency is uncertain, but it is generally considered to be rare. ITAC has a unique and interesting relationship to occupational exposure to wood and/or leather dust [28, 29]. This has been most intensely studied in the furniture industry, where individuals are repeatedly exposed to inhaled hard wood. In contrast with SCC (which has the maxillary sinus as its most common site of origin), ITAC shows a predilection for the ethmoid sinus, which accounts for 40 % of cases; other cavities can also be involved, either primarily or secondarily by local extension. Symptoms are non-specific and include nasal obstruction, discharge and proptosis, with visual impairment in patients with advanced tumor growth into the orbit.

Several classification systems have been used. The most common classification refers to four separate subtypes [28]: papillary (papillary architecture with occasional tubular glands, minimal cytologic atypia, and rare mitotic figures); colonic (tubulo-glandular architecture, increased nuclear pleomorphism and mitotic activity; Fig. 7); solid (solid and trabecular architecture); and mucinous (abundant mucus, either intracellular or as large lakes containing small floating nests of tumor cells). Combinations of mixed subtypes also occur. The most common subtypes associated with wood workers as well as sporadic cases are the papillary and colonic. The tumors show a characteristic pattern of CK7, CK20, CDX2 and MUC immunoreactivity, which can be used for their precise characterization.

Molecular investigations have been undertaken in a few studies and shown that ITAC shows a similar molecular profile to typical colon cancer. They show *APC* and *KRAS* mutations, but they have not been found to show the high level of microsatellite instability that has been associated with Lynch Syndrome [30–32].

Intestinal-type adenocarcinomas are treated by complete surgical resection, usually followed by radiotherapy. Survival rates are in a range of 60 % at 5 years and depend on disease extent and histologic subtype. Recently, exposure to environmental (tobacco) and occupational (metal dust) factors were also identified to be of prognostic importance [33].

Non-intestinal type adenocarcinoma

Adenocarcinomas that do not show the features of an ITAC or other defined salivary-type adenocarcinoma are collectively known as non-ITAC. These tumors show a wide age-range and can range from low to high-grade variants [29]. Clinical symptoms are similar to those already mentioned for other sinonasal malignancies. There is no evidence supporting an environmental etiology.

Histologically, low-grade non-ITAC shows various architectural patterns ranging from tubular and simple glandular, to papillary or cystic. Most of the tumors in this category tend to show a rather monotonous population of columnar cells (Fig. 8). A tubulopapillary low-grade variant has also been reported [34]. High-grade non-ITAC will often show a more solid growth pattern with necrosis, cellular pleomorphism and a high mitotic rate. Residual glandular/luminal differentiation will allow for differentiation from SNUC.

Overall prognosis for non-ITAC sinonasal adenocarcinoma is estimated at a 5-year survival of 60 %, but is dependent on grade. High-grade tumors show a 3-year survival as low as 20 % [17], whereas low-grade tumors are relatively indolent. Treatment also varies accordingly to grade: low grade tumors might be treated solely with surgical excision, while extensive lesions of higher histologic grade, which have a greater risk of recurrence, may require radiotherapy [29].

Recently, it has been suggested that low grade non--ITAC may have some relationship with respiratory epithelial adenomatoid hamartoma, a polypoid growth containing glands with ciliated respiratory epithelium [35].

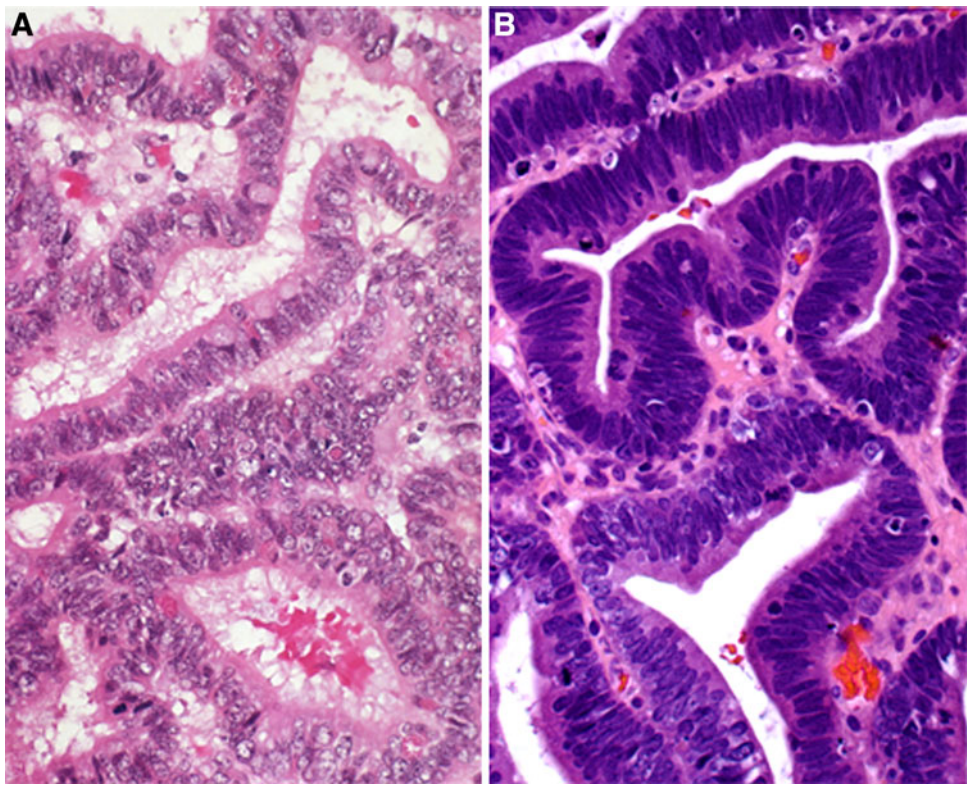

Fig. 7 Intestinal type adenocarcinoma; **A** colonic type and **B** papillary-colonic type show ribbons of columnar cells

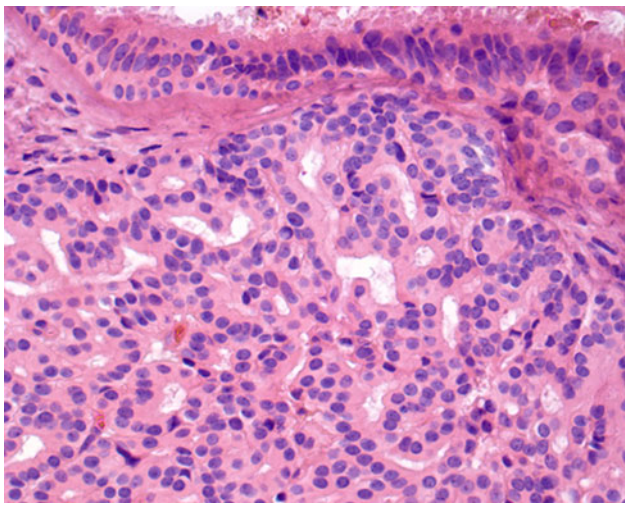

Fig. 8 Adenocarcinoma non-intestinal: closely packed glands lined with monotonous cells

Sinonasal renal cell-like adenocarcinoma

Since the original description, four additional cases have been added to the literature [36, 37]. This is an extremely unusual sinonasal neoplasm that histologically simulates renal cell carcinoma. There is no gender predilection, with a mean age at presentation of 50 years. These tumors arise in nasopharynx or nasal cavity.

Histologically, the tumors are composed of clear cells that are arranged in solid or glandular patterns (Fig. 9). There is no mucous or squamous differentiation. The differential diagnosis includes other clear cell neoplasms, such as SCC with clear cell change, clear cell mucoepidermoid carcinoma, salivary clear cell (hyalinizing) carcinoma and metastatic clear cell variant of thyroid carcinoma (papillary or follicular). However, metastatic renal cell carcinoma is the main differential diagnosis and should be excluded. Immunohistochemistry can distinguish between these two tumors. A useful panel will include vimentin, renal cell antigen (RCC), PAX8, and CK7. Vimentin and RCC are usually expressed in conventional clear cell renal cell carcinoma, but are not seen in sinonasal renal cell-like adenocarcinoma.

The clinical course seems to be favorable, with no reports of metastatic disease or recurrences after surgery or radiotherapy in the few described cases, which may preclude the need for aggressive multimodal therapeutic algorithms [37].

Small cell neuroendocrine carcinoma

This is part of a spectrum of neuroendocrine carcinomas, which also includes carcinoids and atypical carcinoids. As both types of carcinoid are extremely rare in the sinonasal tract, they are not further discussed.

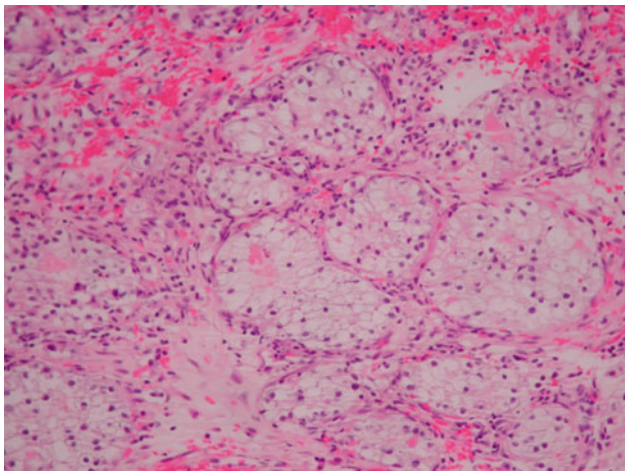

Fig. 9 Sinonasal renal cell like adenocarcinoma characterized by the presence of nests of clear cells. Picture courtesy of M. Brandwein-Gensler, University of Alabama at Birmingham, USA

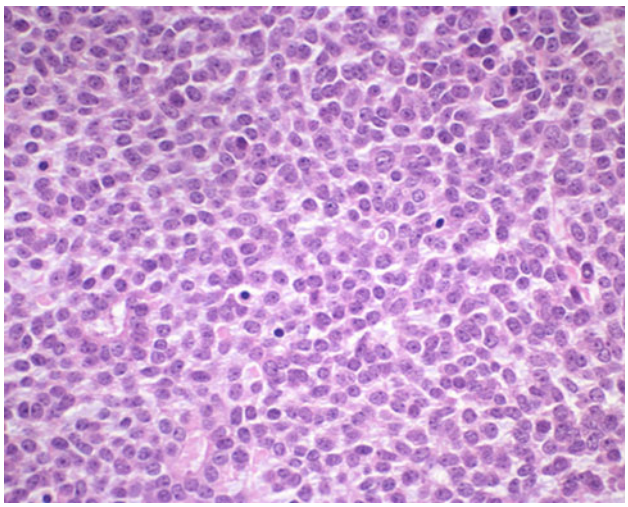

Fig. 10 Sinonasal neuroendocrine carcinoma shows nuclei with the fine granular chromatin typical of neuroendocrine differentiation

Small cell neuroendocrine carcinoma arises mainly at the superior or posterior nasal cavity with extension into adjacent sinuses and skull base. While there is destructive growth, the onset is usually not rapid. There is no gender predilection and the age at diagnosis ranges from 3rd to 8th decade. Symptoms are non-specific, those of a space-occupying sinonasal mass.

Histologically, the tumor is composed of cells with inconspicuous cytoplasm and nuclei with dense chromatin and small nucleoli. Necrosis is frequently seen along with a high mitotic count/proliferation index (Fig. 10). Immunohistochemically, the tumor cells are positive for cytokeratins, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), synaptophysin, chromogranin, CD56 and neuron specific enolase, but negative for TTF1, CD99, FLI1 and pituitary hormones. This immunoprofile allows distinction from SNUC and other small blue round cell tumors that may occur in the sinonasal tract [21, 22].

Small cell neuroendocrine carcinoma has a poor prognosis, which corresponds with the clinical profile of small cell carcinoma arising at other sites. These tumors show high rates of local and regional recurrences, and distant failure [38–40]. In one series, nine out of 21 patients died within 4 years [41]. Treatment strategies incorporating induction chemotherapy followed by concomitant chemoradiation have been introduced recently.

Olfactory neuroblastoma

Olfactory neuroblastoma, also known as esthesioneuroblastoma, represents 6 % of sinonasal malignancies [17]. It can be seen at any age, with a bimodal peak in the 3rd and 6th decades. There has been a suggestion (though largely un-proven to date) that these two peaks reflect two separate entities. Most cases are located at the roof of the nasal cavity, with the tumor originating from and involving the cribriform plate of the ethmoid sinus. An ectopic origin elsewhere in the sinonasal tract is extremely rare [15]. Clinical symptoms are non-specific [42]. MRI using T1-weighted post-Gadolinium contrast shows a hyperintense mass that involves the cribriform plate and extends both to the ethmoid sinus and anterior skull base, the appearances being regarded as characteristic.

Histologically, the tumor appears as a lobular/nested, cellular growth in fibrous, vascular stroma. The tumor has a propensity to track underneath a usually intact and uninvolved surface epithelium (Fig. 11). A diffuse growth pattern is uncommon. Four grades have been suggested, according to Hyam's system [42]. Grade I shows lobules of uniform, rounded tumor cells with small round nuclei, fine dispersed ("salt-and-pepper") chromatin and inconspicuous nucleoli. Mitoses are infrequent and necrosis is not seen. Delicate neurofibrillary material may accumulate between cells. In grade II tumors, neurofibrillary matrix is less obvious, the nuclei show pleomorphism and there is increased mitotic activity. Grade III tumors retain a lobular architecture, but show further increase of mitotic activity, anaplastic/hyperchromatic nuclei and little or no neurofibrillary matrix. Grade IV tumors are also arranged in a lobular architecture, but pleomorphic nuclei with prominent eosinophilic nucleoli are often seen. Necrosis is common and neurofibrillary matrix is absent. In practice, it may be difficult to distinguish between Grade II and III tumors and the rarity of the tumor increases the difficulties. Presence of Homer Wright pseudorosettes and Flexner–Wintersteiner true neural rosettes has been reported in up to 30 % and less than 5 % of cases respectively [42]. Their diagnostic significance may have been overemphasized.

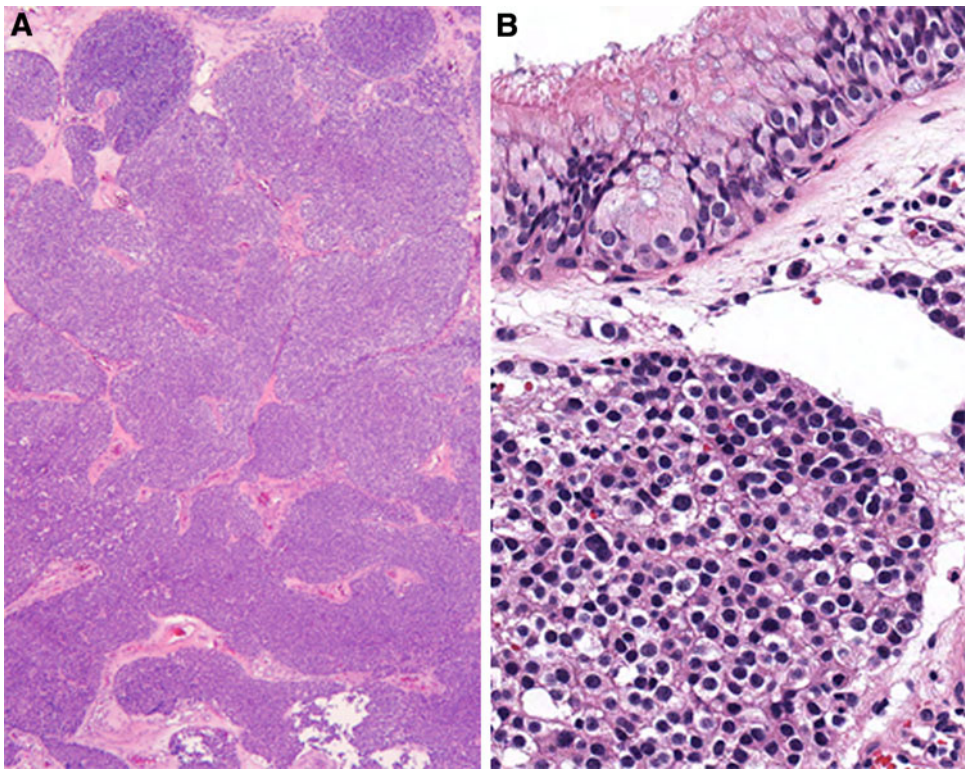

Fig. 11 Olfactory neuroblastoma: (**A**) low power view shows lobular architecture while (**B**) the high power view, shows monotonous cells and relationship with overlying epithelial lining

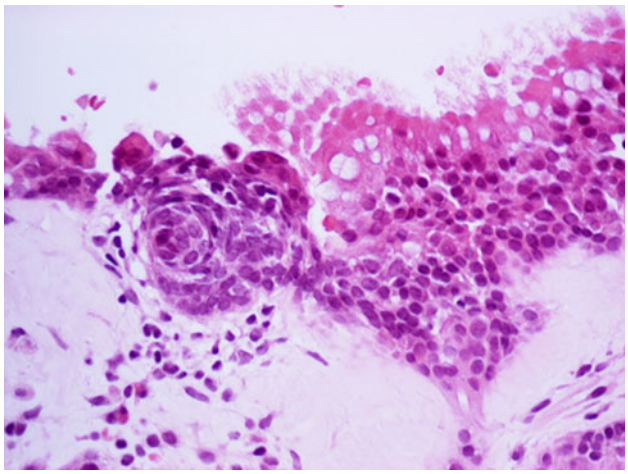

Fig. 12 Intraepithelial/in situ component of olfactory neuroblastoma. The tumor cells are arranged as variously whorled aggregates and focally extend along the lining of a glandular duct. Invasive tumor is present at the right lower corner of the picture. Cilia of surface epithelial cells are easily seen

Little or no attention has been paid to an intraepithelial/in situ component, but it may be detected (Fig. 12).

Elongated cells at the periphery of the lobules, so-called sustentacular cells, are demonstrable on immunohistochemistry for S100 protein or glial fibrillary acidic protein (GFAP) and are often very useful for the diagnosis. Unfortunately, however, they may be inconspicuous or only focally seen in high-grade tumors. The tumor cells are immunoreactive for typical neuroendocrine markers, including synaptophysin, chromogranin, CD56, and CD57. Cytokeratin, FLI1 and CD99 may be focally expressed. Staining for EMA, CEA and hematologic as well as myogenic markers is negative [21, 22, 42]. Recently, calretinin positivity has been suggested as a useful marker [43].

The differential diagnosis of olfactory neuroblastoma includes SNUC, lymphoma, rhabdomyosarcoma, mucosal malignant melanoma, Ewing sarcoma/PNET, neuroendocrine carcinoma and even paraganglioma. Of greatest significance is the distinction from small cell neuroendocrine carcinoma. Small cell neuroendocrine carcinomas do not usually show a lobular and nested pattern, and are frequently of a higher cytologic grade than most typical olfactory neuroblastomas. Immunohistochemistry may be useful in high-grade cases, particularly the demonstration of foci of S100 protein-positive sustentacular cells. Keratins are less useful as some expression may occur in olfactory neuroblastoma. Recent reviews give a good overview on the application of immunohistochemistry in distinguishing olfactory neuroblastoma from other undifferentiated sinonasal neoplasms [21, 22, 42]. The molecular genotype of olfactory neuroblastomas has not been extensively studied. One recent investigation indicated that the tumor often show a complex pattern of gene losses/gains. Specific mutations have not been reported [44].

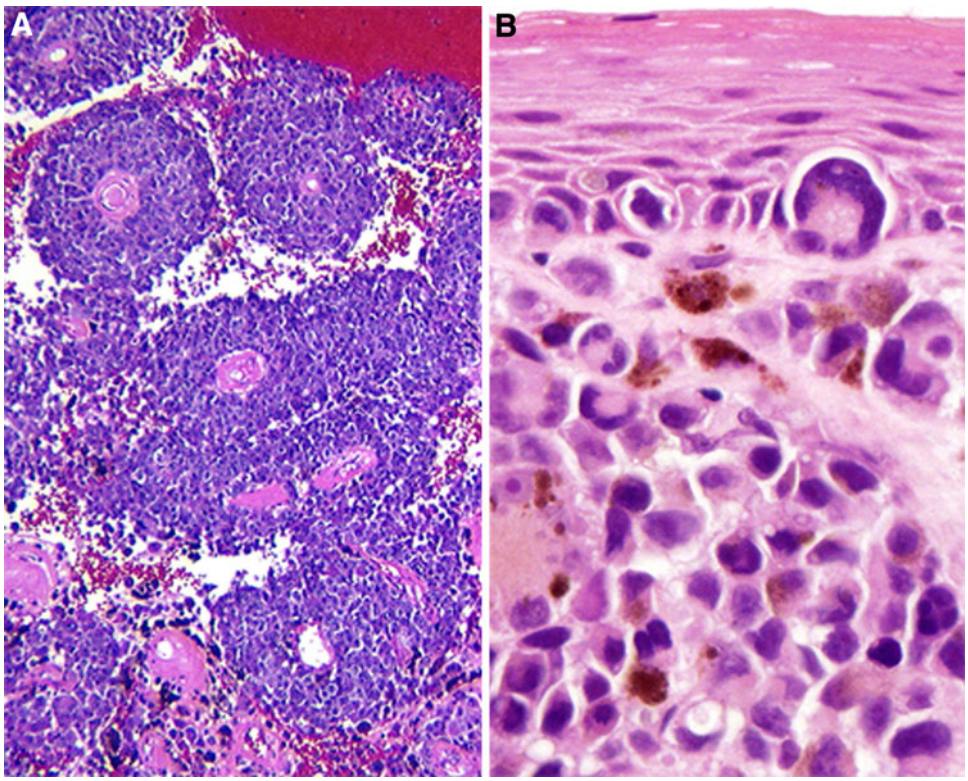

Fig. 13 Melanoma: (**A**) low power view shows large sheets of poorly differentiated cells. (**B**) At higher magnification epithelioid cells with melanin pigment can be seen as well as contact with overlying squamous epithelium. Coarse pigment granules are within accompanying macrophages

For the entire group of olfactory neuroblastoma, a 5-year survival rate of 70 % has been reported [17]. When grades are considered, the 5-year survival ranges from 80 % (low-grade tumors) to 40 % (high-grade tumors). Local recurrence and cervical lymph nodal and distant metastases are known to occur [42]. Tumor stage affects survival [45]. Combined surgery and radiotherapy are mainstays of treatment and recently the role of chemotherapy as a determinant of a subsequent local therapy has been explored [46, 47].

Malignant melanoma

Malignant melanomas arising in the sinonasal mucosa are rare, accounting for less than 5 % of all sinonasal tract tumors [48]; in one large series, they account for 7 % of all sinonasal malignancies [15]. Clinical symptoms are those of any space occupying mass in the tract, although melanorrhea is unique. Grossly, sinonasal melanomas can range in appearance from flat and pigmented in situ lesions, to the more typical large polypoid mass lesion of advanced disease.

Histologically, the tumor cells are highly variable as with melanomas of skin. The cytology can range from epitheloid to spindle-shaped, and varying degrees of pigmentation are seen. Cytoplasmic melanin is not always present and pigmented tumor cells may be less coarsely granulated than accompanying melanophages. The tumor cells typically show pronounced atypia, mitotic activity and prominent eosinophilic nucleoli (Fig. 13). Fascicular and peritheliomatous (Fig. 14) arrangements are frequent [49]. Immunohistochemically, the tumor cells show expression of HMB45, melan-A and S100 protein. Positivity for neuroendocrine markers may be a feature [21, 22]. Demonstration of an intraepithelial or in situ component (Fig. 15) would support the primary nature of the tumor. However, this may be difficult in large and ulcerated tumors and in those cases detailed history and clinical examination would be of help in excluding metastasis.

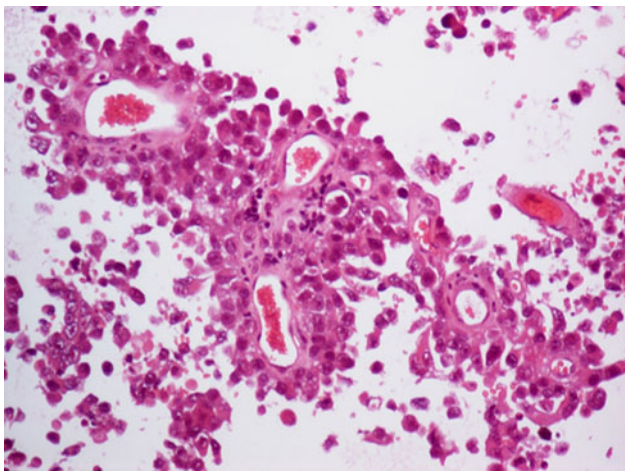

Fig. 14 Peritheliomatous arrangement of sinonasal malignant melanoma

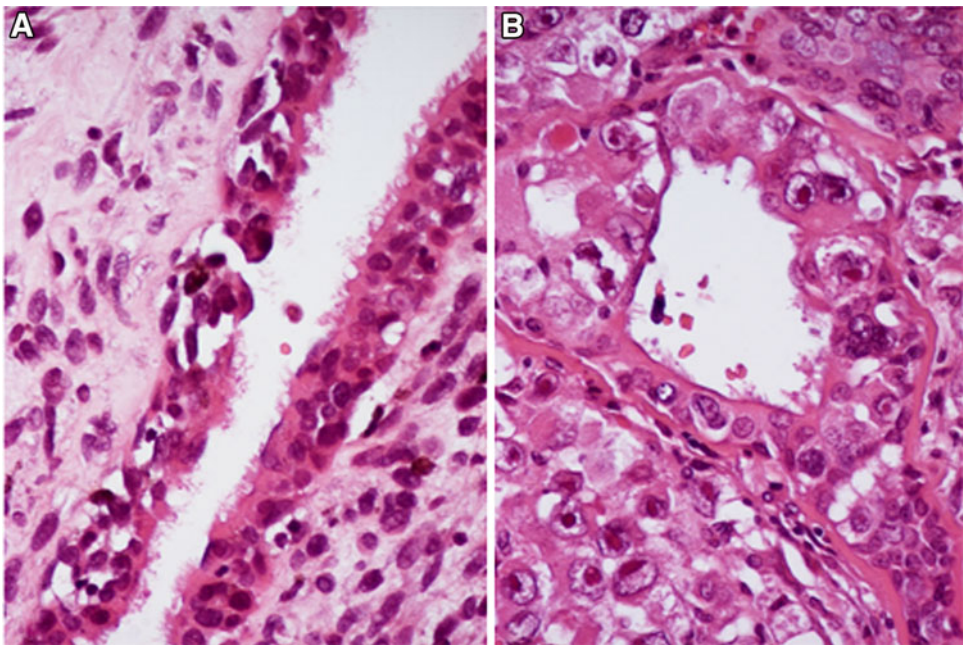

Fig. 15 Intraepithelial/in situ component of sinonasal malignant melanoma. Intraepithelial atypical melanocytes affected by retraction artefact, and arranged in nests and parallel to the surface (**A**). Intraepithelial epithelioid atypical melanocytes with prominent nucleoli. Narrow, hyalinised stroma is discernible between in situ and invasive tumor. Ciliated cells are seen (**B**)

The molecular profile of melanomas in both sun-exposed and mucosal sites has been under intense investigation recently. In contrast to skin-based melanomas, mucosal melanomas do not show nearly as high a rate of *BRAF* gene mutations [50]. There is, however a subset of mucosal melanomas that show mutations of the *c-KIT* gene [51–53]. Loss of p16 expression is a frequent event in sinonasal melanoma and it is mainly related to 9p21deletions. At variance with cutaneous melanoma, loss of p16 is not correlated with the prognosis of sinonasal melanoma [54].

Sinonasal melanomas are locally aggressive lesions, with local recurrences, cervical nodal and distant metastasis resulting in a poor 5-year survival of approximately 25 % [55]. Surgery continues to play a major role in the treatment of sinonasal melanoma [56]. Due to the inherent difficulty in obtaining clear margins in sinonasal tumors, adjuvant radiotherapy is often recommended. Unfortunately, the positive effect on local control is not reflected in the improved survival of melanoma patients. However, radiotherapy alone may be the only treatment option for unresectable tumors [57].

Tumors not arising from the mucosal surfaces

Glomangiopericytoma

Glomangiopericytoma was previously known as sinonasal-type hemangiopericytoma [58] and represents a rare sinonasal neoplasm.

Histologically, the tumor consists of packed cells in fascicular, storiform, whorled or palisaded arrangements and interspersed with vascular channels in a so-called "staghorn" pattern (Fig. 16). Perivascular hyalinization is characteristic, along with extravasated erythrocytes, eosinophils and mast cells. Despite its former designation, the tumor is not related to hemangiopericytoma of soft tissues, a lesion now regarded as part of the solitary fibrous tumor spectrum. The strong CD34 immunoreactivity that is the hallmark of solitary fibrous tumor is not seen in glomangiopericytoma, which instead shows reactivity for smooth muscle actin and factor XIIIa.

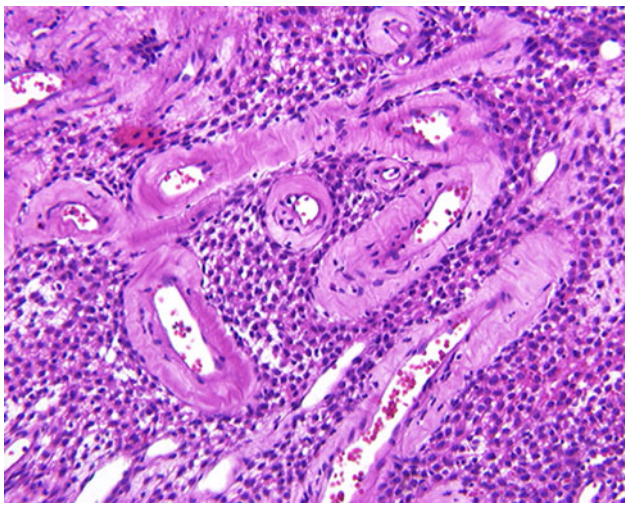

Fig. 16 Glomangiopericytoma is characterized by the presence of sheets of monotonous cells that surround vessels which show a characteristic peritheliomatous hyalinization

Although it has been suggested that glomangiopericytoma should be differentiated from other spindle cell

tumors of the sinonasal tract, the histology is rather characteristic and, once the possibility is considered, diagnosis is easy with immunohistochemistry being confirmatory [59].

Glomangiopericytoma has a 5-year survival greater than 90 %, but tends to recur in 7–40 % of cases. Tumors over 5 cm that invade bone and show nuclear pleomorphism, necrosis and a high mitotic rate are more likely to behave aggressively [59]. Consequently, although prognosis is excellent, strict follow-up is required, especially if complete resection is not achieved [60].

Extranodal NK/T-cell lymphoma, sinonasal type

In Northern Mediterranean countries, B-cell lymphomas may account for as much as 50 % of all sinonasal lymphomas [61], but overall, it is the extranodal NK/T celllymphoma that is the most common and distinctive lymphoma type in the sinonasal tract [62]. It is characterized by a diffuse, cellular infiltrate causing swelling of the nasal or paranasal sinus mucosa. Angiocentricity, angiodestruction and fibrinoid deposits in vessel walls are common and result in extensive secondary inflammation, necrosis and ulceration. This may mask the neoplastic nature of the lesion and cause diagnostic difficulties, particular when small/superficial biopsies are taken. Such biopsies may be reported as non-diagnostic, but a useful diagnostic criterion would be the detection of vascular "ghosts'' within necrotic material (Fig. 17). The progressive ulceration and necrosis that characterize these tumors are not seen in B-cell lesions. There is often severe destruction of the nasal septum and facial midline structures which account for now obsolete, though historically interesting, terms such as "lethal midline granuloma" or "rhinitis gangrenosa progressiva" [63].

Immunohistochemistry shows that many NK/T-cell lymphomas express CD2, and CD56. CD3 is seen in the cytoplasm, but not on the cell surface. Most cases are also positive for cytotoxic granule associated proteins (granzyme B, TIA-1 and perforin). These lymphomas typically lack CD16 and CD57, and usually lack other T antigens such as CD4, CD5, CD6, CD7, CD8TCRb and TCRδ. CD43, CD45RO, and HLA-Rd are commonly expressed. Occasional cases are positive for CD30 [64].

Practically all cases are associated with Epstein Barr virus (EBV) demonstrable with the use of EBV encoded RNA (EBER) in situ hybridization. The procedure allows visualizing tumor cells against a background of extensive secondary inflammation and excludes the possibility of Wegener's granulomatosis which may be considered in the differential diagnosis [65].

Historically, overall survival for this type of lymphoma was poor with a 5-year overall survival rate of only 30–40 %, but it has recently improved substantially with more intensive therapy including up-front radiotherapy [66–68].

Recently, an intramucosal variant of this lymphoma has been reported with a more favorable prognosis than the more common invasive type [69].

Sinonasal teratocarcinosarcoma

Sinonasal teratocarcinosarcoma (SNTCS) is a malignant neoplasm with features of teratoma and carcinosarcoma. This entity was first defined by Shanmugaratnam et al. in

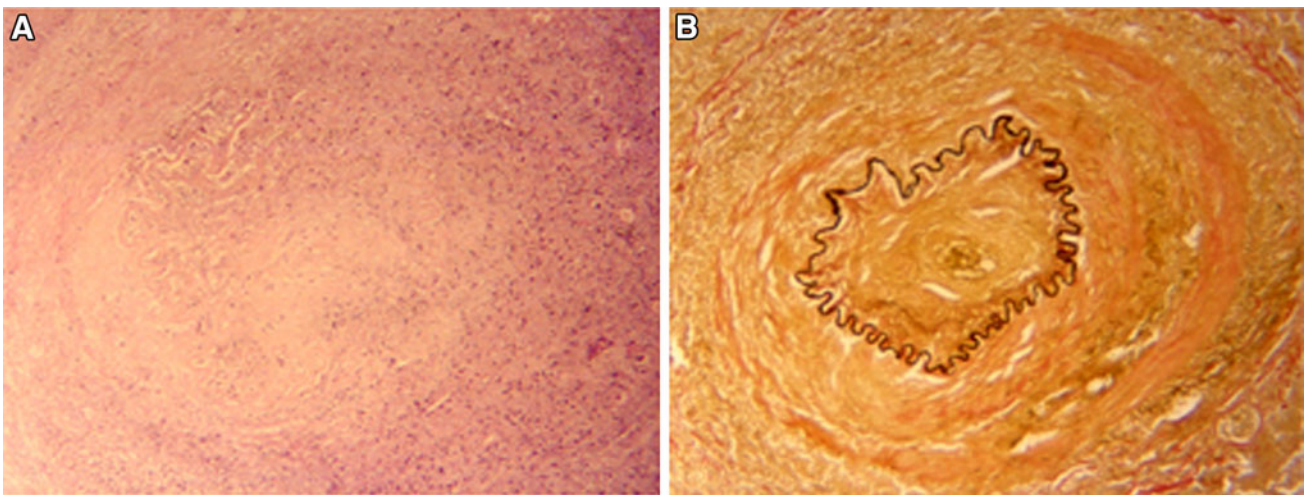

Fig. 17 Sections from a small, superficial, intranasal biopsy. The resistant, internal elastic lamina of a destroyed muscular artery is discernible within eosinophilic, necrotic material mixed with hematoxyphilic cell debris (**A**). Adjacent section specially stained with elastic van Gieson stain to demonstrate the elastic lamina. On the basis of this finding the surgeon was alerted to the possibility of underlying, extranodal NK/T-cell lymphoma (**B**). A deeper, more substantial biopsy of viable tissue confirmed the diagnosis

1983 [70]. Knowledge on SNTCS was expanded by Heffner and Hyams in 1984 [71]. A clear cut distinction between SNTCS and other sinonasal germ cell tumors was provided by the WHO in 2005 [72]. Benign and malignant epithelial, mesenchymal, and neural elements are typically present, as well as immature tissues with blastomatous features, all of which blend in complex architectural arrangements providing a unique histological appearance (Fig. 18). "Fetal-appearing" clear cell squamous epithelium is a common finding and an important diagnostic clue. Neuroepithelial elements with rosettes and neuroblastoma-like areas are present in most instances. Areas of embryonal carcinoma, choriocarcinoma, seminoma, or yolk sac tumor are absent in SNTCS [71]. Immunohistochemical findings may vary according to the tissue components found [73].

SNTCS is a very rare neoplasm [74]. It almost exclusively arises in the ethmoid sinus and in the maxillary antrum, although a few SNTCSs have been reported to arise in the roof of the nasopharynx [71], sphenoid sinus [75], and pharynx [76].

Patients have an age range between 18 and 79 years (mean 60 years), and there is a male predominance [71]. Primary symptoms are nonspecific with a short history of nasal obstruction and epistaxis produced by a nasal cavity mass [71].

The exuberant tissue heterogeneity of SNTCS is behind the many pitfalls faced when only dealing with small biopsies. This could lead to such mistaken diagnoses as olfactory neuroblastoma, SCC, undifferentiated carcinoma, adenocarcinoma, malignant salivary gland-type tumors and adenosquamous carcinoma [71].

It has been suggested that SNTCS probably arises from a primitive cell in the olfactory/sinonasal membrane that not only reproduces the neuroectodermal features of olfactory neuroblastoma, but also has the capacity to differentiate into divergent types of somatic cells [73]. Quite recently trisomy 12 and 1p deletion have been identified in SNTCS, which is supportive of germ cell origin [77].

SNTCSs are locally aggressive tumors, with rapid invasion of soft tissues and bone, and metastasis to regional lymph nodes and sites, such as the lung. The average

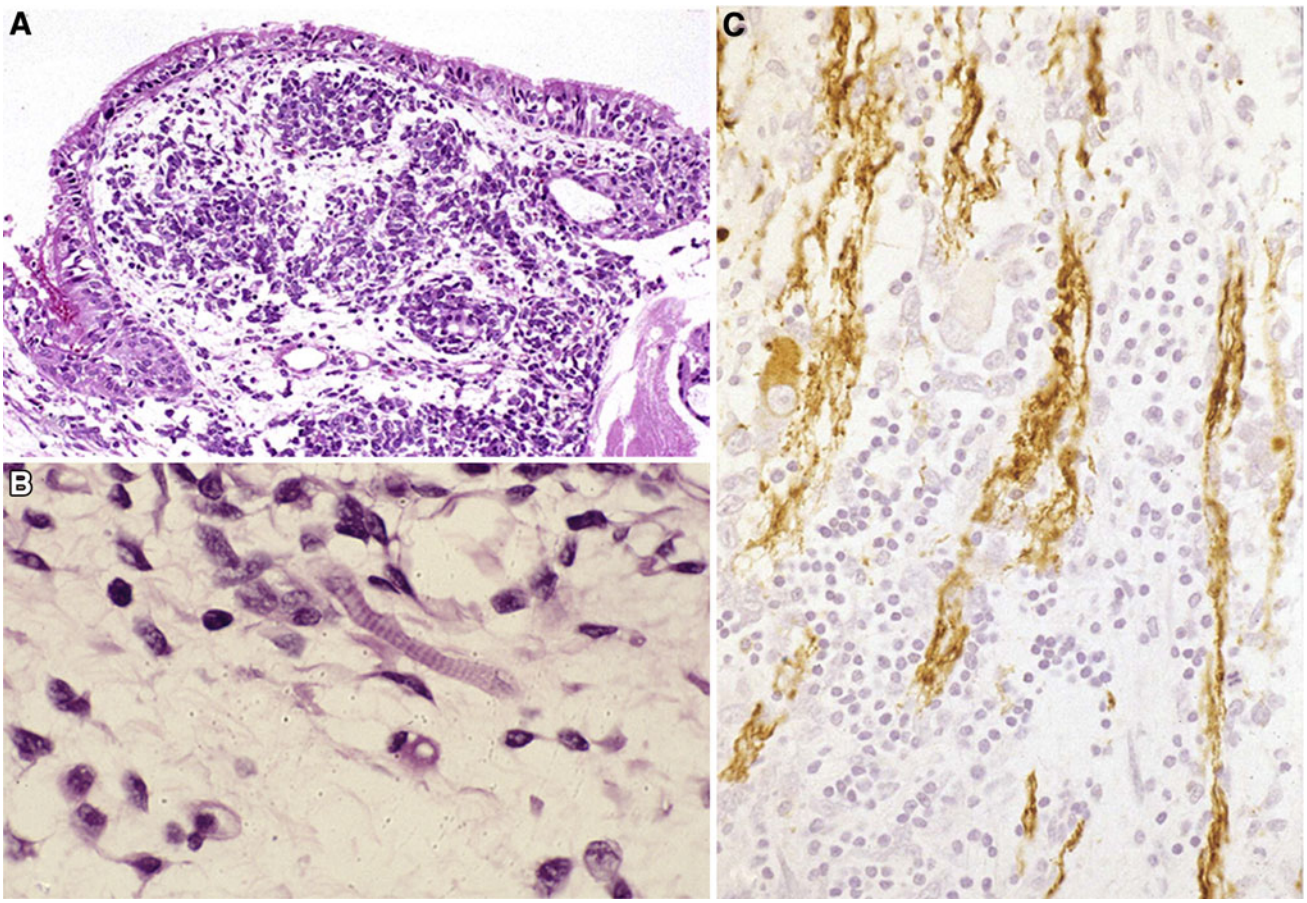

Fig. 18 Sinonasal teratocarcinosarcoma. Low power view showing polypoid tissue mass covered with respiratory epithelium (**A**). High-power view showing rhabdomyomatous differentiation (**B**). Immunohistochemical demonstration of neurofilament expression indicates neurogenic differentiation (**C**)

survival of SNTCS is 1.7 years, with 60 % of the patients not surviving beyond 3 years. The treatment of SNTCS is controversial, but an aggressive initial therapeutic approach with a combination of surgical resection, radiotherapy and chemotherapy is usually recommended [78]. Chemotherapy-induced neuronal maturation has been recently documented in SNTCS [79].

Tumors involving the sinonasal tract by local extension

Occasionally, tumors arising from adjacent sites may manifest as growths of the sinonasal tract. Among these, chordoma and craniopharyngioma usually involve the ethmoid sinuses or the roof of the nasal cavity, pituitary adenoma involves the sphenoid sinus, whereas odontogenic tumors arising in the maxilla (in most cases ameloblastoma or odontogenic myxoma) obliterate the maxillary sinus by local extension. These should be included in the differential diagnosis of sinonasal tumors when appropriate.

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