



MINI-SYMPOSIUM: HEAD AND NECK PATHOLOGY

Sinonasal carcinomas

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Lymphoepithelial carcinoma;
Olfactory neuroblastoma;
Sinonasal undifferentiated carcinoma

Summary Malignant neoplasms of the sinonasal tract encompass a wide variety of epithelial, lymphoid and mesenchymal tumours. The separation and classification of epithelial or neuroepithelial tumours is sometimes challenging, especially when treatment and prognosis are different. Squamous cell carcinoma, keratinizing or non-keratinizing and, usually, the poorly differentiated type need to be separated from sinonasal undifferentiated carcinoma, lymphoepithelial carcinoma, neuroendocrine carcinoma and olfactory neuroblastoma. Whereas melanoma and lymphoma are also included in the broad differential, along with primitive neuroectodermal tumours and rhabdomyosarcomas, the focus of this commentary will be to present the major clinical, radiographical, histological, immunohistochemical, ultrastructural and molecular features which allow for separation of the principle mucosal epithelial neoplasms of the sinonasal tract.

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Introduction

Malignant sinonasal tract tumours comprise <1% of all neoplasms and about 3% of those of the upper aerodigestive tract.¹ Squamous cell carcinoma (SCC) and adenocarcinoma are strongly associated with environmental factors, including tobacco, alcohol and occupational exposure (e.g. to heavy metal particles such as nickel and chromium) and with workers in the leather, textile, furniture and wood industries.^{1–5}

Sinonasal tract malignancies most commonly affect the maxillary sinus (about 60%), followed by

the nasal cavity (about 22%), ethmoid sinus (about 15%) and frontal and sphenoid sinuses (<3%). Sinonasal tract tumours are diverse, with the majority being SCC and its variants (55%), followed by non-epithelial neoplasms (20%), glandular tumours (15%), undifferentiated carcinoma (7%) and miscellaneous tumours (3%).^{1,3–5} Carcinoma of the nasopharynx differs in many aspects from that of the nasal cavity and paranasal sinuses and will not be discussed herein. Furthermore adenocarcinomas including salivary gland-type carcinomas and non-epithelial tumours will not be discussed.

The clinical presentations, radiological features and pattern of tumour spread for SCC, adenocarcinoma and most of the other malignant neoplasms of the sinonasal tract are similar. Gross appearance of

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the sinonasal tract and nasopharyngeal malignancies has limited value in aiding diagnosis, because the initial diagnosis depends on the tissue obtained by endoscopy or polypectomy. The treatment of choice for most sinonasal tract carcinomas is surgical resection with clear margins.^{1,3-5} The following discussion will focus on the specific clinical, radiographical and diagnostic criteria used in the separation of selected carcinomas of the sinonasal tract, specifically sinonasal undifferentiated carcinoma (SNUC), small cell carcinoma, lymphoepithelial carcinoma (nasopharyngeal-type) and neuroendocrine carcinoma (Table 1). In this context, a brief discussion about SCC is necessary

to establish the criteria for separation from these different tumour types.

Squamous cell carcinoma

Clinical features

SCC has a male predilection (2:1), with a peak incidence in the sixth–seventh decades. The location, in the order of frequency, is maxillary sinus, nasal cavity, ethmoid sinus, frontal sinus and sphenoid sinus.^{1,3-5} Early diagnosis is difficult

Table 1 Comparison of sinonasal malignant neoplasms.

Feature	Squamous cell carcinoma	Sinonasal undifferentiated carcinoma	Lymphoepithelial carcinoma	Neuroendocrine carcinoma	Olfactory neuroblastoma
Mean age (years)	55–65	55–60	40–60	50	40–45
Site	Nasal cavity and/or sinuses	Multiple sites usually	Nasal cavity > sinuses	Superior/posterior nasal cavity, ethmoid, maxillary sinuses	Roof of nasal cavity
Radiographical studies	Little destruction/spread	Marked destruction/spread	May invade palate, orbit, base of skull	May invade skull base or orbit	'Dumbbell-shaped' cribriform plate mass
Prognosis	60% 5-year (stage and tumour type dependent)	< 20% 5-year survival	Favourable with radiotherapy	> 60% die of disease	60–80% 5-year survival
Cranial nerve involvement	Uncommon	Common	Can be present	Uncommon	Sometimes
Pattern	Syncytial	Sheets and nests	Islands, sheets	Ribbons, islands	Lobular
Cytology	Squamous differentiation, keratinization, opaque cytoplasm	Medium cells, inconspicuous nucleoli	Large, vesicular nuclei and prominent nucleoli	Salt and pepper, granular chromatin	Salt and pepper chromatin, small nucleoli (grade dependent)
Anaplasia	Present	Common	Syncytial with moderate atypia	Moderate	Occasionally and focally
Mitotic figures	Present	High	Present	High	Variable
Necrosis	Limited	Prominent	Focal to absent	Prominent	Occasionally
Vascular invasion	Rare	Prominent	Uncommon	Present	Occasionally
Neurofibrillary stroma	Absent	Absent	Absent	Absent	Common
Pseudorosettes	Absent	Absent	Absent	Present	Common
Keratin	Positive	> 90%	Positive	Positive	Focal, weak
CK 5/6	Present	Negative	Positive	n/a	Negative
EMA	Present	50%	Positive	n/a	Negative
NSE	Negative	50%	n/a	Positive	> 90%
S-100 protein	Negative	< 15%	n/a	Positive	+ (sustentacular)
Synaptophysin	Negative	< 15%	Negative	Positive	> 90% (can be weak)
In situ EBER	Absent	Absent	Positive	Absent	Absent
Neurosecretory granules (EM)	Absent	Rare	Absent	Present	Numerous

EMA, Epithelial membrane antigen; NSE, neuron-specific enolase; EBER, Epstein–Barr virus encoded early RNA; EM, electron microscopy.

because symptoms and signs are non-specific and closely resemble those of chronic sinusitis, allergic reaction and nasal polyposis. Initial symptoms are related to the effects of the mass causing unilateral nasal obstruction. Secondary infection is common, giving rise to a mucoid or purulent discharge. Epistaxis develops when the mucosa is ulcerated or tumour extends into the sinus wall. Tumours involving the ethmoid, maxillary, or frontal sinuses may cause proptosis, restriction of eye motility, diplopia or loss of vision. Epiphora results from lacrimal sac or duct obstruction by the tumour. Compression of the nerve at the primary site or perineural space invasion can compromise the functions of cranial nerves.^{1,5} A mass or discoloured lesion may be visualized endoscopically and biopsied.

Late manifestations include facial swelling and cheek paraesthesia resulting from anterior maxillary extension into the soft tissue and infraorbital nerve involvement, respectively. Inferior extension into the oral cavity forms a visible mass in the palate or alveolar ridge. Posterior extension can cause trismus from pterygoid muscle invasion. Ear symptoms suggest possible involvement of the nasopharynx, eustachian tube and pterygoid plates. Upward extension into the skull base may lead to cranial nerve involvement and dura invasion. In the initial work-up, it is rare to find cervical lymph node metastasis.^{1,3-5}

Radiological features

Computer tomography (CT) and magnetic resonance imaging (MRI) have largely replaced conventional radiographs in imaging sinonasal tract disease. CT and MRI complement each other, helping to separate inflammatory disorders and benign and malignant neoplasms and to provide pretreatment information, including location, size, extent, local invasion, regional and distant metastasis. Of particular interest is tumour extension into the pterygopalatine and infratemporal fossae, as well as the relationship between the tumour and the blood vessels (especially the internal carotid artery and cavernous sinus), nerves and cranial cavity. CT highlights bony structures, with bony destruction and soft tissue invasion usually being indicative of an aggressive lesion. MRI is superior to CT in its ability to delineate sinus tumours from inflammatory disease and it can better delineate tumour from the adjacent soft tissues. Using MRI, inflamed mucosa, polyps and non-inspissated secretions, with a high water content, have high signal intensity on T2-weighted images. In contrast, cellular paranasal neoplasms have lesser amounts

of water and demonstrate intermediate signal intensities on T2-weighted images. Perineural spread is best demonstrated using a gadolinium-contrasted MRI and T1-weighted images with fat suppression.¹

Pathological features

Gross findings

Nasal tumours are usually exophytic and prone to become friable, necrotic and ulcerated with increasing tumour size. Sinus tumours may be well-circumscribed, filling the sinus cavity in an expansile fashion with erosion of the bone wall, while others are more destructive, necrotic and haemorrhagic.^{1,3-5}

Microscopic findings

Most authors use a three-grade system based on (1) extent of keratinization, (2) mitotic activity and (3) nuclear features.^{1,5} This grading method correlates to some extent with the tumour behaviour. In general, SCC of the nasal cavity is well-differentiated and keratinizing, whereas sinus counterparts are non-keratinizing and moderately or poorly differentiated (Fig. 1).

SCC is classified by cell type into keratinizing and non-keratinizing.^{1,3} In keratinizing SCCs, the tumour cells exhibit keratinization, intercellular bridges and squamous 'pearls.' Tumour cells usually have enlarged, hyperchromatic nuclei, with a variable degree of nuclear anaplasia. Mitotic figures are usually easy to find (Fig. 2). Stromal invasion by irregular nests and cords of cells in a desmoplastic stroma, which is often associated

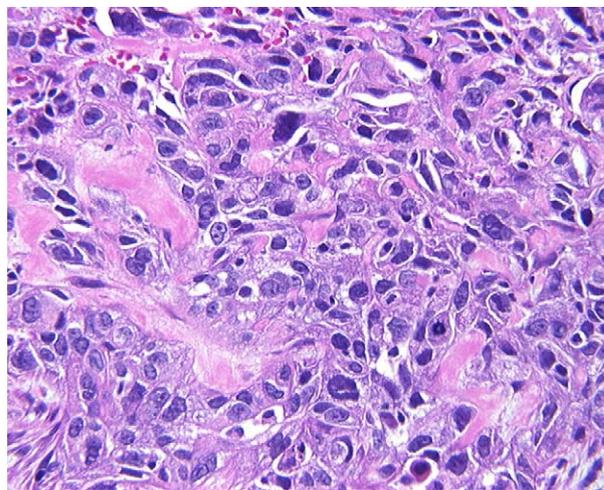


Figure 1 Poorly differentiated squamous cells present with irregular hyperchromatic nuclei, small nucleoli and a moderate amount of cytoplasm. Note increased mitotic figures.

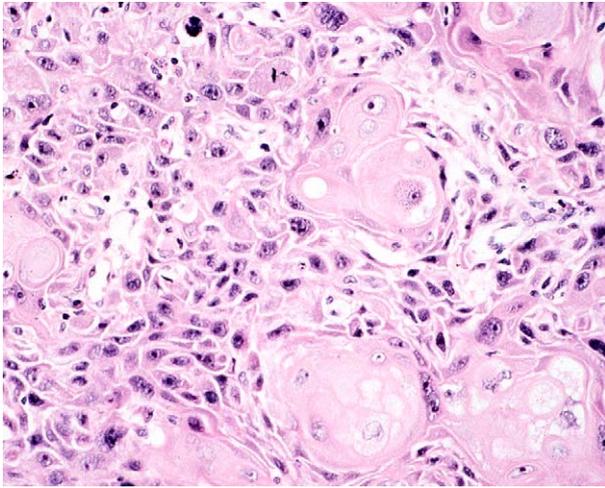


Figure 2 Tumour cells form irregular nests and sheets with keratinizing pearl formation in this keratinizing squamous cell carcinoma (SCC).

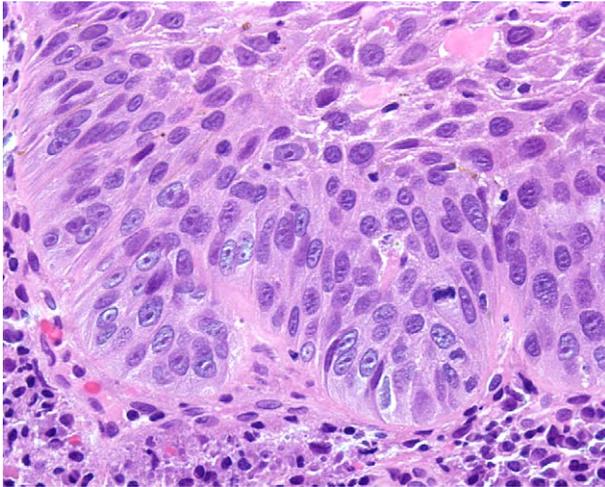


Figure 3 This non-keratinizing squamous cell carcinoma has a smooth border. The cells display prominent nucleoli in cells with identifiable cell borders. A mitotic figure can be seen.

with chronic inflammatory response, can be seen. However, in superficial biopsies, the only sign of stromal invasion may be in the form of single cells becoming isolated from the base of rete pegs or the tip of tongue-like protrusions.

The non-keratinizing type of SCC forms solid nests of variable sizes, frequently with relatively smooth borders. Individual tumour cells reveal uniform large, round, or oval nuclei with prominent nucleoli. The cytoplasm varies from pale acidophilic to amphophilic to vacuolated. The cells may have distinct borders (Fig. 3). Occasionally, individual cell keratinization may be identified. Spindled tumour cells may be seen and, when predominant,

they are diagnosed as spindle cell carcinoma. Papillary and endophytic patterns can be seen. The papillary type has a dysplastic epithelium lining thin fibrovascular cores. The inverted type is usually poorly differentiated, often referred to as 'transitional cell carcinoma,' or 'Schneiderian carcinoma.' The tumour cells are arranged in broad sheets, which have smooth borders and are surrounded by basement membrane-like material. In superficial or small biopsies evidence of stromal invasion is usually absent. In these cases, correlation with radiological evidence of local destruction confirms the invasive nature of the malignancy.¹ Similarly, biopsies of verrucous squamous carcinoma and papillary squamous carcinoma are prone to be under-diagnosed if the base of the lesion is not included (Fig. 4). Variants of SCC, such as verrucous carcinoma and the basaloid type, are rare in the sinonasal tract (Fig. 4).⁶

Ancillary studies

The diagnosis of SCC seldom requires immunohistochemistry, but the cells are CK5/6, CK8 and CK13 positive, while being CK10 negative.^{1,7}

Differential diagnosis

Pseudoepitheliomatous hyperplasia in the sinonasal tract region is most commonly associated with mucosal ulcer, with or without prior medical interventions and may be associated with rhinoscleroma, fungal infection and neoplastic disease.¹ The latter includes granular cell tumour, lymphoma and fibrohistiocytic tumours. The elongated and thickened rete pegs extend into the underlying connective tissue and have smooth, sharp and sometimes pointed borders. There is no desmoplastic stroma. The cells resemble each other and have uniform nuclei without nuclear atypia and rare mitotic figures. Schneiderian and squamous papillomas may occasionally have malignant transformation, with areas of squamous dysplasia and carcinoma in situ. When broad sheets of cytologically malignant squamous cells are seen in biopsies, the diagnosis of SCC should be considered, even though stromal invasion is not demonstrable. Clinical and radiological findings should be requested to aid decision making.^{1,3-5}

Prognosis and therapy

If SCC is confined to the nasal cavity, the 5- and 10-year survival rates are in the range of 80%. Involvement of the paranasal sinus adversely

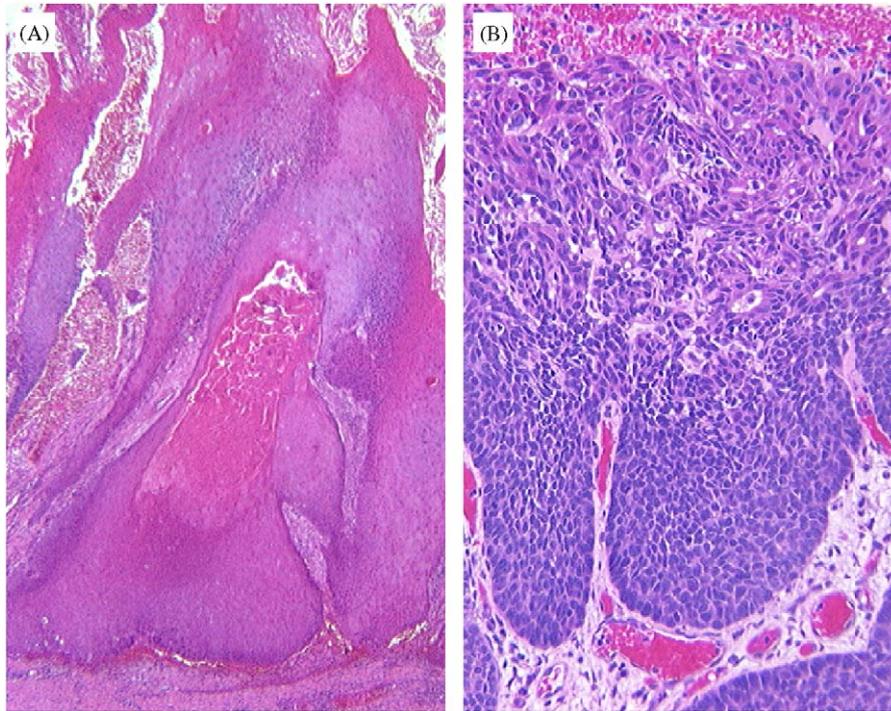


Figure 4 (A) A verrucous squamous cell carcinoma has a broad pushing border of infiltration with parakeratotic crypting, 'church-spire' type hyperkeratosis and bland cytology. (B) A basaloid squamous cell carcinoma has areas of squamous differentiation in a tumour with a predominantly basaloid appearance.

affects the prognosis.^{1,3,4,8} Most treatment failures are related to locally advanced disease and tumour recurrence in areas that are inaccessible to surgical resection, such as the skull base, dura and brain. Cervical lymph node metastasis develops in up to 20% of patients, with rare distant metastases.^{1,5}

Treatment depends on the tumour location and extent.¹ T1 and T2 nasal tumours are treated by surgical resection, while T3 and T4 tumours receive postoperative radiotherapy. Various surgical approaches are employed, with lateral rhinotomy or a mid face degloving for septal tumours, and medial maxillectomy or an en bloc ethmoidectomy for superior and lateral nasal cavity carcinomas. Paranasal sinus tumours are managed by radical en bloc surgical resection (including craniofacial combinations) followed by radiotherapy.^{3-5,8} Chemotherapy may be used as a neoadjuvant or postoperatively.¹

Sinonasal undifferentiated carcinoma

This is a rare and highly aggressive undifferentiated carcinoma, showing pleomorphism and necrosis, but it can be separated from olfactory neuroblastoma (ONB). The taxonomy is not well developed or accepted.⁹

Clinical features

This type of undifferentiated carcinoma is a distinct clinicopathological entity.¹⁰ The majority of patients present with locally advanced disease with frequent bony, cranial or orbital involvement at diagnosis. The median age is in the sixth decade with a male predominance (2–3:1). Previous radiation may be an aetiological factor. Patients have non-specific symptoms, indistinguishable from other sinonasal tract tumours. The nasal cavity, maxillary sinus and ethmoid sinus are usually involved, frequently showing spread into directly contiguous sites.⁹⁻¹³

Pathological features

Gross findings

Tumours are usually large (>4cm) with bone invasion and poorly defined margins.¹⁴

Microscopic features

The cells are arranged in nest, lobules and sheets without any squamous or glandular differentiation. The cells have a high nuclear to cytoplasmic ratio with medium-to-large nuclei surrounded by scant cytoplasm. Nucleoli are usually prominent and single (Fig. 5). Necrosis, including comedonecrosis

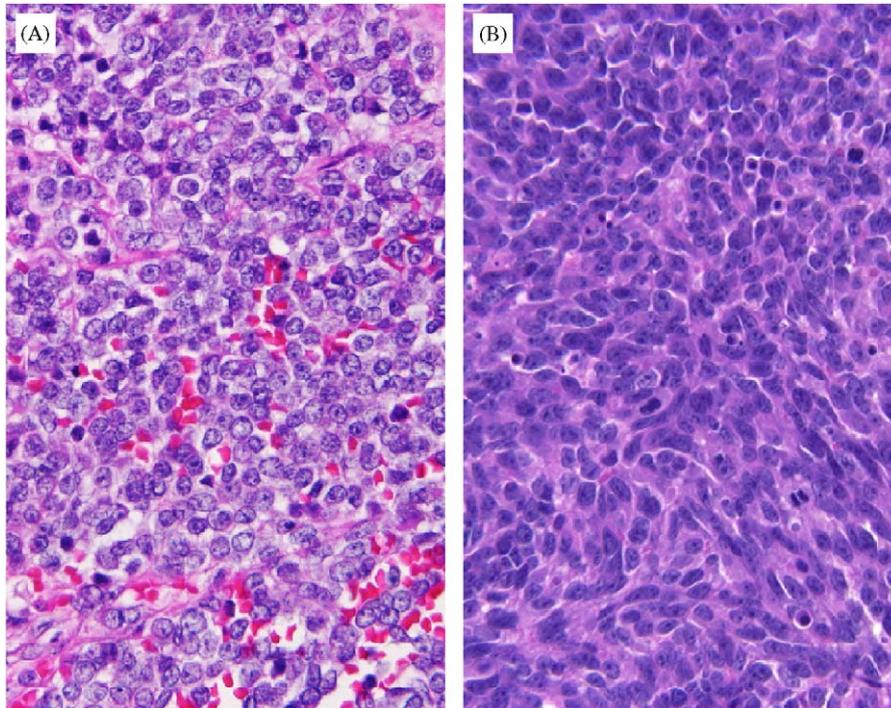


Figure 5 SNUC. (A) A sheet of malignant small tumour cells reveal nuclear molding, resulting from high nuclear cytoplasmic ratios. (B) The tumour cells have medium-sized round-to-oval hyperchromatic nuclei, a moderate amount of cytoplasm and increased nuclear cytoplasmic ratios.

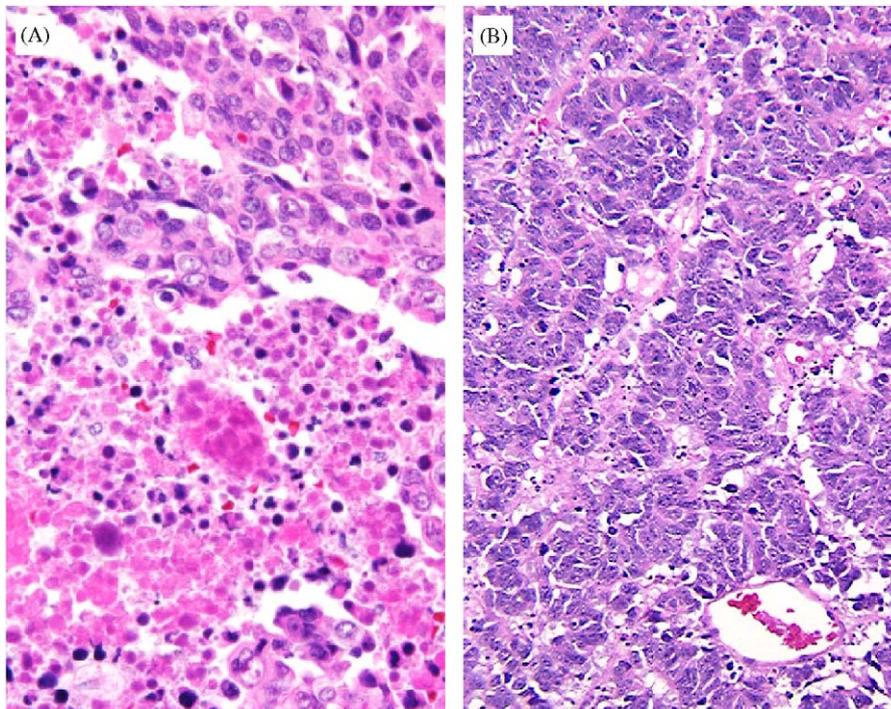


Figure 6 SNUC. (A) Prominent comedo-type necrosis is surrounded by small collections of epithelial cells. (B) Vascular stroma may separate the nodules of tumour. Mitotic figures are increased.

is common (Figs. 6 and 7). Mitotic figures are increased. Lymph–vascular invasion is a common finding.^{9,10,12,15–17}

Immunohistochemical features

The majority of tumours react with keratins (especially simple keratins especially (Fig. 8),

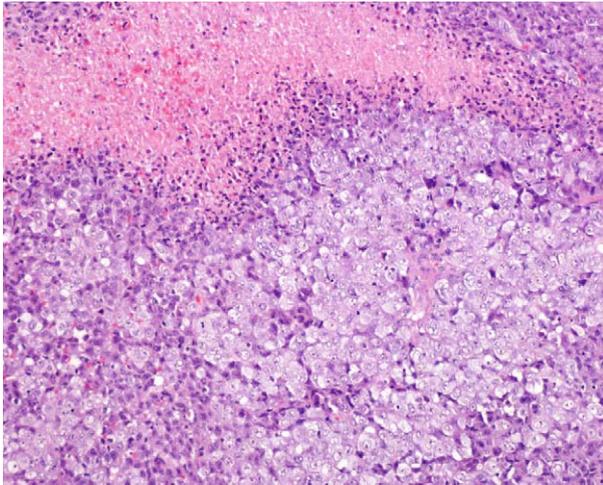


Figure 7 Necrosis is noted in this sinonasal undifferentiated carcinoma in which there is open nuclear chromatin and a sprinkling of inflammatory cells.

CK7, CK8 and CK19). EMA, neuron-specific enolase (NSE) and p53 may be positive. Chromogranin and synaptophysin are rarely positive. Epstein–Barr virus-encoded early RNA (EBER) in situ hybridization is negative.^{7,9,10,12,13,16–20}

Differential diagnosis

Separation of SNUC from ONB and neuroendocrine carcinoma remains controversial (see description of latter, below).^{9,16,17,21}

ONB are thought to arise from the specialized sensory neuroepithelial (neuroectodermal) olfactory cells that are normally found in the upper part of the nasal cavity, including the superior nasal concha, the upper part of the septum, the roof of the nose and the cribriform plate of the ethmoid. This specific anatomical site is almost always requisite (in some part) for the diagnosis. There is a bimodal age distribution in the second and sixth decades of life affecting both genders equally. A 'dumbbell-shaped' mass extending across the cribriform plate is one of the characteristic radiographical findings for this tumour. MRI images with and without contrast will delineate the extent of the disease, with T1-weighted images showing marked enhancement after gadolinium (Fig. 9). The most important histological feature is a lobular

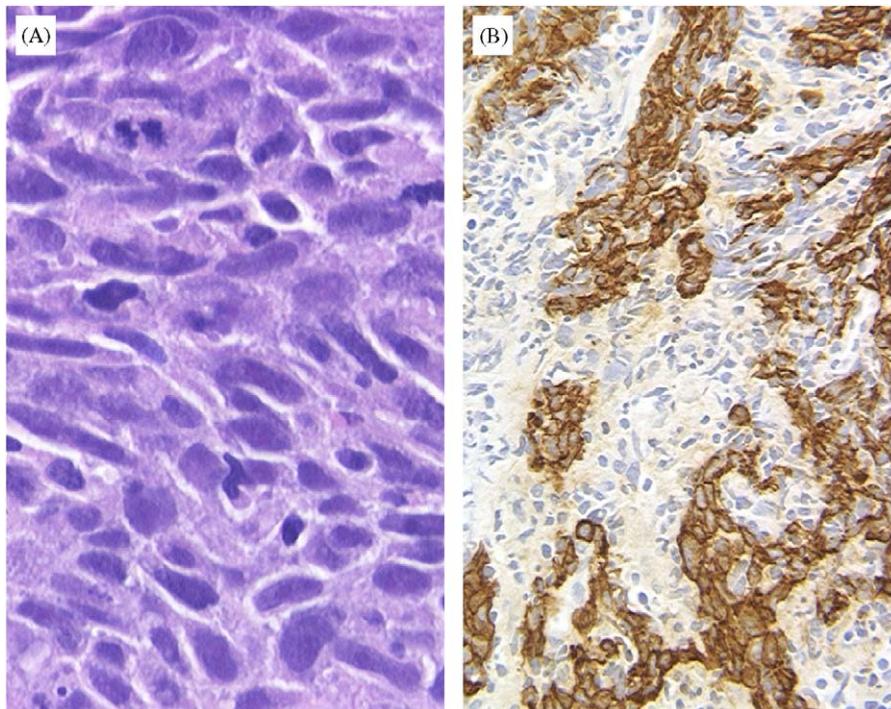


Figure 8 SNUC. (A) Undifferentiated epithelial cells with increased mitotic figures. (B) Keratin immunoreactivity strongly highlights the malignant cells.

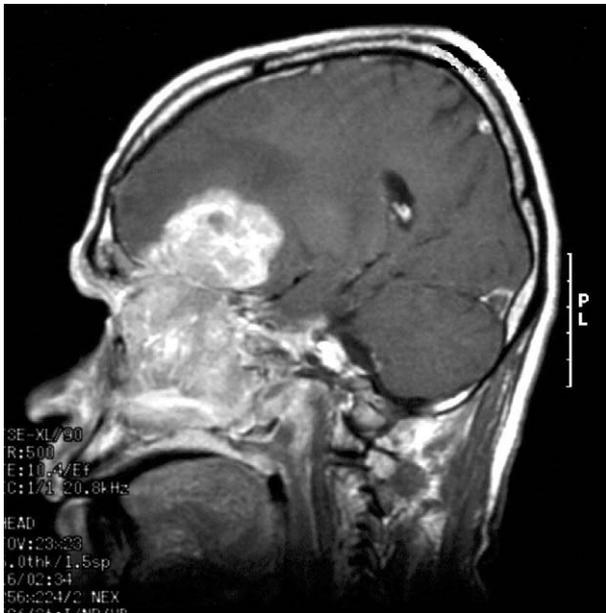


Figure 9 A T1-weighted gadolinium contrast magnetic resonance imaging (MRI) scan shows a dumbbell-shaped mass extending through the cribriform plate and filling the nasal vault and the intracranial cavity.

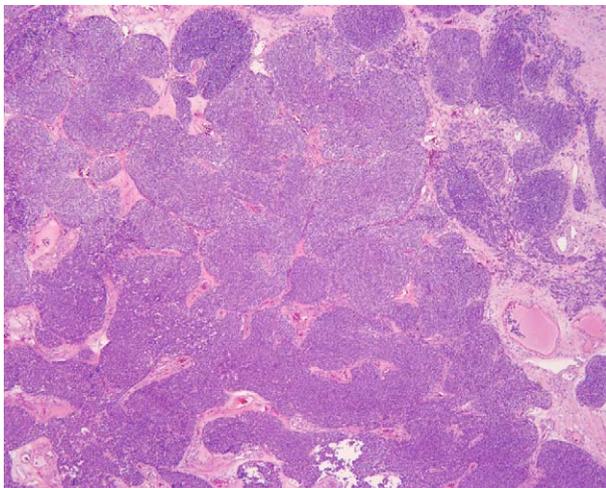


Figure 10 The lobular architectural arrangement of an olfactory neuroblastoma is characteristic and helpful in separating the tumour from other sinonasal tract malignancies.

architecture comprised of 'primitive' neuroblastoma cells. Circumscribed lobules or nests of tumour are identified below the mucosa in a vascularized fibrous stroma (Fig. 10). The tumour cells are 'small, blue, round' cells that are slightly larger than mature lymphocytes, with a very high nuclear to cytoplasmic ratio. The nuclei are small and uniform with hyperchromatic, albeit delicate, uniform nuclear chromatin distribution. Nucleoli are

inconspicuous. The cells are often in a syncytial arrangement with a tangle of neuronal processes forming the background (Fig. 11). While high-grade lesions exist, for the most part, nuclear pleomorphism, mitotic figures (>2 /high-power field (HPF)) and necrosis are uncommon. Two types of rosettes are seen, although only in up to 30% of cases. Pseudorosettes (Homer Wright) are more common and true rosettes (Flexner–Wintersteiner) are less common. The delicate, neurofibrillary and oedematous stroma forms in the centre of a cuffing or palisaded arrangement of cells in Homer Wright pseudorosettes, while a 'gland-like' tight annular arrangement is seen in Flexner–Wintersteiner-type rosettes (Fig. 12). As ONBs become higher grade, pseudorosettes and fibrillar stroma are less common. The nuclei become more pleomorphic, chromatin is coarser, mitotic figures increase and tumour necrosis is present. Tumours are graded, based on the degree of differentiation, presence of neural stroma, mitotic figures and necrosis, from Grades 1 to IV, which correlates with prognosis.^{15,21–25} ONBs are positive for synaptophysin, chromogranin and NSE, with S-100 protein-positive cells being found at the periphery of the tumour lobules and corresponding to Schwann (sustentacular) cells. A few cells within ONBs may also stain with low molecular weight cytokeratins. However, it is never to the extent seen in SNUCs.^{21,26} The absence of the EWS/FLI-1 gene fusion, t(11; 22)(q 24;q12) translocation and CD 99 expression indicate that the ONB is not related to the Ewing/PNET group of tumours.²⁷

Prognosis and therapy

Prognosis is usually poor, with a median survival of <18 months. Overall survival is about 20% at 5 years.^{9–12,15,28} There is frequent recurrence with metastasis to lymph nodes and distant sites. A combination of radical surgery, chemotherapy and radiotherapy provides the best chance of survival.²⁹

Lymphoepithelial carcinoma

The nomenclature for carcinomas of the nasopharynx has undergone several iterations, but a 'lymphoepithelial' carcinoma of the sinonasal tract has recently been accepted as a distinct entity, separated from nasopharyngeal carcinoma by topography, but still similar histologically.^{30,31} In the past 'undifferentiated carcinoma' and 'lymphoepithelioma-like carcinoma' have been used as synonyms, but these terms have now been

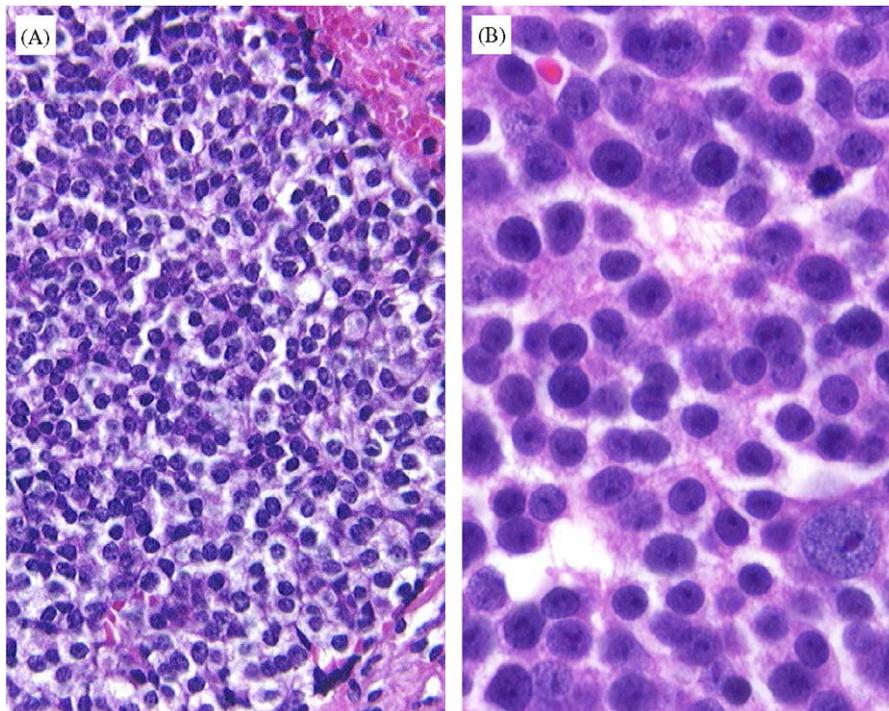


Figure 11 ONB. (A) Small blue round cells with a high nuclear to cytoplasmic ratio comprise olfactory neuroblastoma. (B) A high power shows that the nuclear chromatin is coarse and granular and contains small-to-medium sized nucleoli in this Grade 2 neoplasm. Pseudorosettes can be seen.

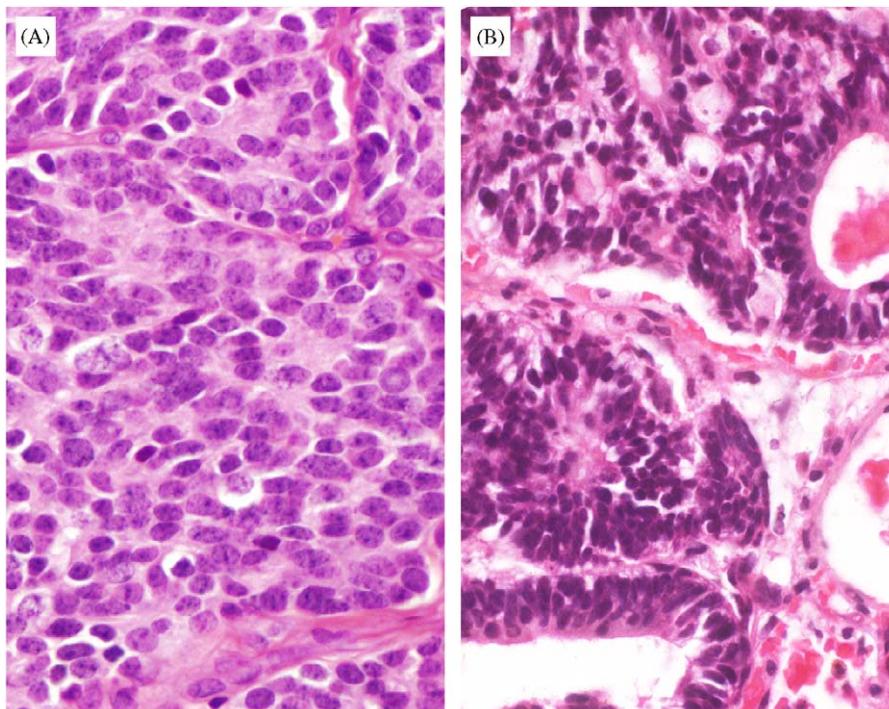


Figure 12 (A) Homer Wright pseudorosettes with neural tangles in the centre of a syncytium of syncytial cells. (B) Flexner-Wintersteiner true rosettes with a 'gland-like' arrangement and inspissated material.

abandoned in favour of lymphoepithelial carcinoma for this type, in order to separate it from SNUC.

Clinical features

This type of carcinoma is extremely uncommon in the sinonasal tract, with the majority of cases identified in Southeast Asian countries (Thailand, Philippines, Vietnam, China), similar to its morphological analogue of the nasopharynx.³² There is a strong aetiological association with Epstein–Barr virus (EBV) (especially early antigen and viral capsid antigen).^{30–32} Men are affected more commonly than women (3:1), with a wide age range at initial presentation, although adults in the fifth–seventh decades seem to be affected most often. The nasal cavity is affected most often, followed by the paranasal sinuses, although both may, rarely, be affected. The tumour may invade into the adjacent bony structures of the palate, orbit and skull base. Patients present with non-specific symptoms, with cranial nerve palsies if there is cranial vault extension. Occasionally, lymph node metastases to the cervical chain may be the initial presenting symptoms.^{30–32} While axiomatic, exclusion of a nasopharynx primary with direct extension into the sinonasal tract is prudent.³² Both CT and MRI are used in assessing the local extent of the tumour for treatment planning.

Pathological features

The World Health Organization (WHO) histological typing system uses criteria similar to those for nasopharyngeal carcinoma of the non-keratinizing type for this anatomical site.^{30–32} The tumour is arranged in irregular islands, solid sheets, trabeculae and single neoplastic cells. The neoplastic cells are intimately intermingled with lymphocytes and plasma cells (Fig. 13). The cells are syncytial-appearing, with large tumour cells lacking cell borders. The nuclei are usually vesicular with large, central, prominent nucleoli (Fig. 14). Sometimes a greater degree of 'differentiation' is appreciated with cellular paving and stratification. While mitotic figures are easy to find, *necrosis* and *keratinization* are not. A desmoplastic stroma is uncommon. The lymphoid component is often less heavy than the counterpart in the nasopharynx. Tumour cells may, uncommonly, be spindled. In metastatic deposits, the lymphoid mixture is similar to the primary, although a desmoplastic stroma and epithelioid granulomas may obscure the metastatic foci.³²

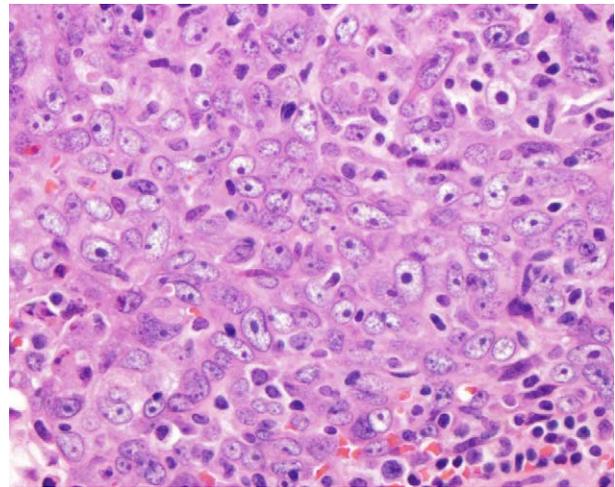


Figure 13 This lymphoepithelial carcinoma has a characteristic syncytial architecture with large nuclei containing vesicular nuclear chromatin and prominent nucleoli. Lymphocytes are present in the background.

Ancillary studies

The tumour cells can be confirmed as epithelial with a strong and diffuse reaction with pan-keratin (Fig. 14), often highlighting wisps of cytoplasm in a reticular pattern as they surround lymphocytes (if present).⁷ Epithelial membrane antigen can be used as an alternative. EBV is found in nearly 100% of tumours, most reliably detected using the in situ hybridization technique for EBER, which will show strong nuclear labelling in nearly all tumour cells.^{7,30–32} The lymphoid cells react with a compartmentalized mixture of B- and T-cells, supporting a reactive population.

Differential diagnosis

Histological separation of lymphoepithelial carcinoma from SNUC, lymphoma, Hodgkin lymphoma and malignant melanoma is essential as each of these lesions has a different treatment and outcome.^{30,31} SNUC tends to be much more pleomorphic, has central necrosis, is a bulky tumour and tends to have a high mitotic index. Most SNUCs are EBV-negative, although this finding should not be solely relied upon in Asian patients.^{32,33} Immunohistochemical stains are essential for reaching a definitive diagnosis for separation between a lymphoma and a melanoma (Fig. 15). Hodgkin lymphoma is uncommon in the sinonasal tract, but Reed–Sternberg cells should be identified with appropriate confirmatory immunohistochemistry.

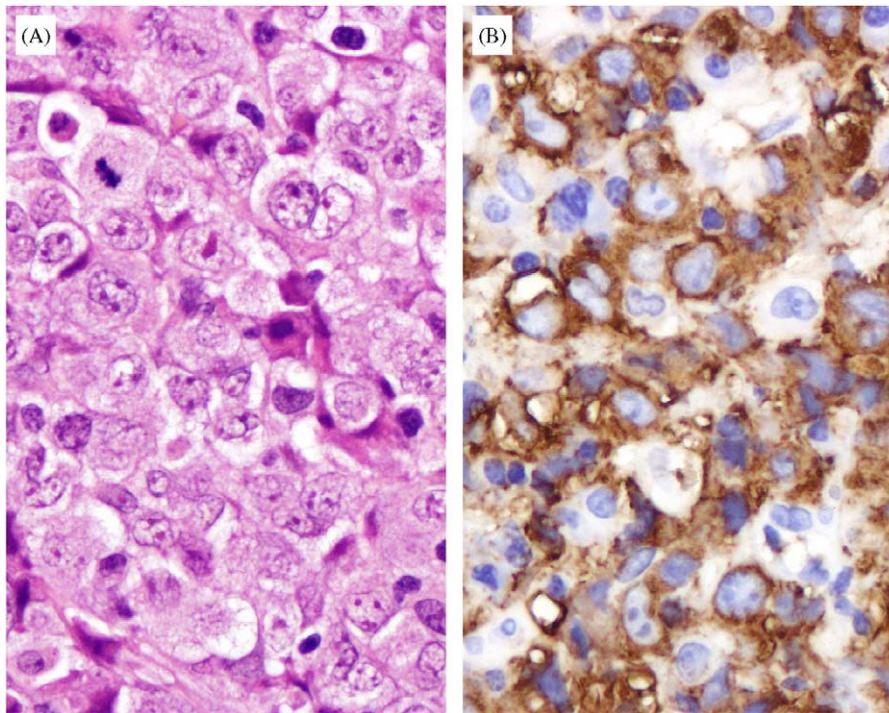


Figure 14 Lymphoepithelial Carcinoma. (A) Vesicular nuclear chromatin in cells that lack borders in this lymphoepithelial carcinoma. (B) Strong and diffuse keratin immunoreactivity highlights the neoplastic cells in a background of lymphocytes.

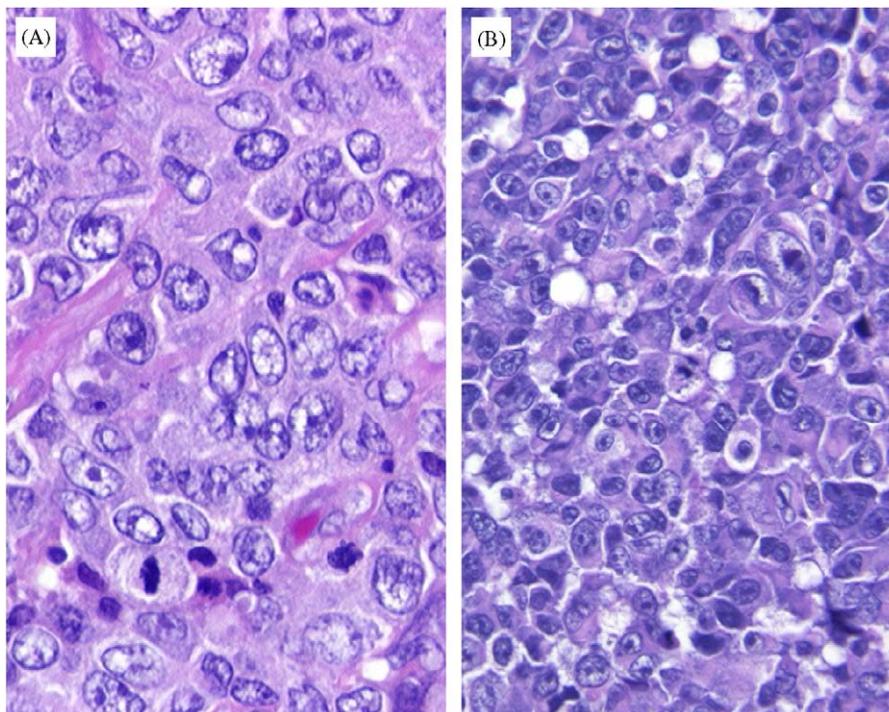


Figure 15 (A) A diffuse, large B-cell lymphoma can mimic a lymphoepithelial carcinoma, although it will be immunoreactive with lymphoid markers. (B) A mucosal melanoma may also come into the differential diagnosis, but is usually not syncytial, lacks vesicular nuclear chromatin, tends to have a plasmacytoid appearance and may have pigment.

Prognosis and therapy

The prognosis is stage-dependent. Radiation is the cornerstone of therapy, even when there is lymph node metastasis. However, when distant metastases develop, often to bone and lungs, the prognosis declines substantially. With extensive or advanced disease, chemotherapy may be added (pre-, concurrent, or post-radiation). Post-therapy biopsies are sometimes difficult to interpret, especially if taken within 3 months of therapy. Maintenance of the nuclear to cytoplasmic ratio favours reactive changes. In situ EBER reaction would favour residual/recurrent tumour. In some cases, monitoring the EBV DNA titre may suggest disease relapse, although it is usually a late finding.^{30–32}

Neuroendocrine carcinoma

Neuroendocrine carcinomas are very rare in the nasal cavity, paranasal sinuses or nasopharynx. The recognizable types are carcinoid, atypical carcinoid and small cell carcinoma neuroendocrine type.^{16,17,34–38} A few cases may not fit these categories and the diagnostic label 'neuroendocrine carcinoma, not otherwise specified' may be applied.

Clinical features

Neuroendocrine carcinomas in the nasal cavity and paranasal sinuses are exceedingly rare, although possibly under-reported due to inclusion in other categories. There is a wide age range at presentation with non-specific symptoms of nasal obstruction, epistaxis, facial mass and/or facial pain. There is no known association with smoking or radiation exposure.^{36,37,39} Most tumours arise in the nasal cavity but may extend into adjacent sinuses.³⁸ High-grade tumours can be seen in the sinuses only, without nasal cavity involvement.^{39,40} Extensive involvement including the skull, orbit and brain may be seen.^{36,40} Rarely, hormone production may be revealed by elevated serum levels (ACTH, calcitonin, ADH).³⁵

Pathological features

Neuroendocrine tumours are usually unencapsulated, covered by an uninvolved, although frequently ulcerated, surface mucosa. The tumours present with a variety of different histological patterns, including organoid, trabecular, cords,

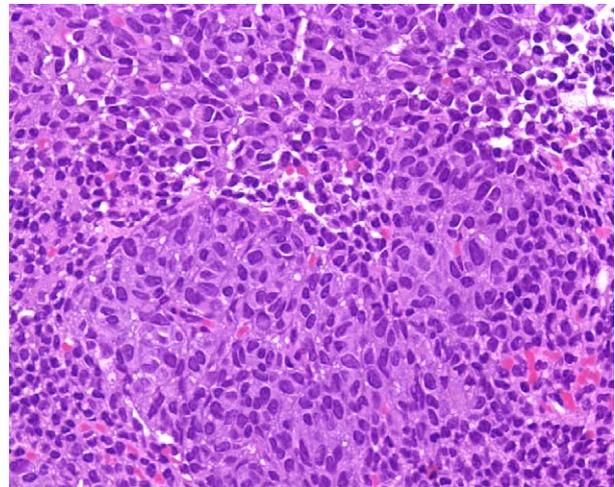


Figure 16 Lobules of a neuroendocrine carcinoma mimic the features seen in other sinonasal tract neoplasms.

sheets (Fig. 16), ribbons, pseudoglands and rosette formations (Fig. 17), cribriform, solid and single-file patterns. Lymph-vascular, perineural and soft tissue invasion is common.³⁸ Tumour cell spindling may be present. The degree of cellular pleomorphism, mitotic activity and necrosis increases as the tumour becomes more poorly differentiated (small cell carcinoma). The tumour cells vary from small, monotonous cells with round vesicular nuclei with stippled chromatin (carcinoid) to cells with a high nuclear-to-cytoplasmic ratio and intensely hyperchromatic oval-to-spindled nuclei without nucleoli (Fig. 16). There is extensive necrosis, apoptosis and mitoses in small cell carcinoma.^{16,17,35,41} Neural matrix is absent. Due to the fragility of the cells, crush artefact is frequently prominent in small cell carcinoma. Glandular (with mucin production) or squamous differentiation can be seen in neuroendocrine neoplasms.

Ancillary studies

All grades of tumour variably react with keratin, EMA, CEA, chromogranin (Fig. 17) and synaptophysin, while other neuroendocrine and hormone markers are variably reactive (neuron specific enolase, Leu 7, neurofilaments proteins, calcitonin).³⁵ Almost all of these lesions are non-reactive for S-100 protein, GFAP and met-enkephalins.^{16,17,19,26,42}

Differential diagnosis

An important differential diagnosis is ONB.^{16,17,34,41} ONBs occur in a specific anatomical site, tend to be lobular, have neural matrix in the background and

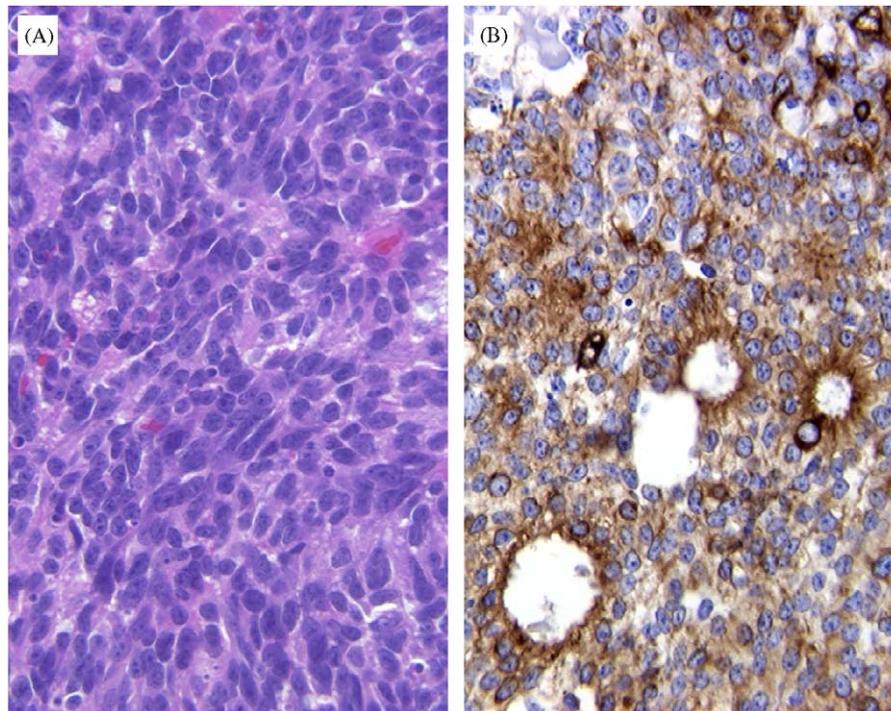


Figure 17 (A) A sheet-like to pseudorosette pattern can be seen in neuroendocrine carcinomas. (B) Strong and diffuse immunoreactivity for chromogranin, highlighted around the apical region of the cells as they form rosettes.

will lack keratin reactivity (in the majority of cells), while demonstrating sustentacular S-100 protein reactions.¹⁹ Separation from SNUC may be made with sheet-like architecture of larger cells, with prominent nucleoli and vascular invasion. However, absolute separation between these tumour types may be impossible in certain cases. Using 'carcinoma with neuroendocrine features' may be appropriate in these cases.

Prognosis and management

Neuroendocrine carcinomas are locally aggressive to highly aggressive neoplasms with frequent local recurrence and distant metastasis with a poor prognosis notwithstanding multimodal therapy. The majority of patients die of their disease, although 5-year survival is reported.^{35,36,38–40,43}

References

- Pilch BZ, Bouquot J, Thompson LDR. Squamous cell carcinoma. In: Barnes EL, Eveson JW, Reichart P, Sidransky D, editors. *Pathology and genetics of head and neck tumours*. (Kleihues P, Sobin LH, series editors. *World Health Organization classification of tumours*.) Lyon, France: IARC Press; 2005. p. 15–17.
- Luce D, Leclerc A, Begin D, et al. Sinonasal cancer and occupational exposures: a pooled analysis of 12 case-control studies. *Cancer Causes Control* 2002;**13**:147–57.
- McNicol W, Hopkin N, Dalley VM, et al. Cancer of the paranasal sinuses and nasal cavities. Part II. Results of treatment. *J Laryngol Otol* 1984;**98**:707–18.
- Hopkin N, McNicol W, Dalley VM, et al. Cancer of the paranasal sinuses and nasal cavities. Part I. Clinical features. *J Laryngol Otol* 1984;**98**:585–95.
- Jackson RT, Fitz-Hugh GS, Constable WC. Malignant neoplasms of the nasal cavities and paranasal sinuses: (a retrospective study). *Laryngoscope* 1977;**87**:726–36.
- Wieneke JA, Thompson LD, Wenig BM. Basaloid squamous cell carcinoma of the sinonasal tract. *Cancer* 1999;**85**: 841–54.
- Franchi A, Moroni M, Massi D, et al. Sinonasal undifferentiated carcinoma, nasopharyngeal-type undifferentiated carcinoma, and keratinizing and nonkeratinizing squamous cell carcinoma express different cytokeratin patterns. *Am J Surg Pathol* 2002;**26**:1597–604.
- Carrau RL, Segas J, Nuss DW, et al. Squamous cell carcinoma of the sinonasal tract invading the orbit. *Laryngoscope* 1999;**109**:230–5.
- Frierson HF. Sinonasal undifferentiated carcinoma. In: Barnes EL, Eveson JW, Reichart P, Sidransky D, editors. *Pathology and genetics of tumours of head and neck tumours*. (Kleihues P, Sobin LH, series editors. *World Health Organization Classification of tumours*.) Lyon, France: IARC Press; 2005. p. 19.
- Frierson Jr. HF, Mills SE, Fechner RE, et al. Sinonasal undifferentiated carcinoma. An aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. *Am J Surg Pathol* 1986;**10**:771–9.
- Gorelick J, Ross D, Marentette L, et al. Sinonasal undifferentiated carcinoma: case series and review of the literature. *Neurosurgery* 2000;**47**:750–4.
- Houston GD, Gillies E. Sinonasal undifferentiated carcinoma: a distinctive clinicopathologic entity. *Adv Anat Pathol* 1999; **6**:317–23.

13. Gallo O, Graziani P, Fini-Storchi O. Undifferentiated carcinoma of the nose and paranasal sinuses. An immunohistochemical and clinical study. *Ear Nose Throat J* 1993;72:588–95.
14. Phillips CD, Futterer SF, Lipper MH, et al. Sinonasal undifferentiated carcinoma: CT and MR imaging of an uncommon neoplasm of the nasal cavity. *Radiology* 1997;202:477–80.
15. Miyamoto RC, Gleich LL, Biddinger PW, et al. Esthesioneuroblastoma and sinonasal undifferentiated carcinoma: impact of histological grading and clinical staging on survival and prognosis. *Laryngoscope* 2000;110:1262–5.
16. Mills SE, Fechner RE. 'Undifferentiated' neoplasms of the sinonasal region: differential diagnosis based on clinical, light microscopic, immunohistochemical, and ultrastructural features. *Semin Diagn Pathol* 1989;6:316–28.
17. Ordonez NG, Mackay B. Neuroendocrine tumors of the nasal cavity. *Pathol Annu* 1993;28:77–111.
18. Cerilli LA, Holst VA, Brandwein MS, et al. Sinonasal undifferentiated carcinoma: immunohistochemical profile and lack of EBV association. *Am J Surg Pathol* 2001;25:156–63.
19. Smith SR, Som P, Fahmy A, et al. A clinicopathological study of sinonasal neuroendocrine carcinoma and sinonasal undifferentiated carcinoma. *Laryngoscope* 2000;110:1617–22.
20. Hwang TZ, Jin YT, Tsai ST. EBER in situ hybridization differentiates carcinomas originating from the sinonasal region and the nasopharynx. *Anticancer Res* 1998;18:4581–4.
21. Wenig BM, Dulguerow P, Kapadia SB, Prasad ML, Fanburg-Smith JC, Thompson LDR. Neuroectodermal tumours. In: Barnes EL, Eveson JW, Reichart P, Sidransky D, editors. *Pathology and genetics of tumours of head and neck tumours*. (Kleihues P, Sobin LH, series editors. *World Health Organization classification of tumours*.) Lyon, France: IARC Press; 2005. p. 66–76.
22. Mills SE, Frierson Jr. HF. Olfactory neuroblastoma. A clinicopathologic study of 21 cases. *Am J Surg Pathol* 1985;9:317–27.
23. Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta-analysis and review. *Lancet Oncol* 2001;2:683–90.
24. Lund VJ, Howard D, Wei W, et al. Olfactory neuroblastoma: past, present, and future? *Laryngoscope* 2003;113:502–7.
25. Devaney K, Wenig BM, Abbondanzo SL. Olfactory neuroblastoma and other round cell lesions of the sinonasal region. *Mod Pathol* 1996;9:658–63.
26. Devoe K, Weidner N. Immunohistochemistry of small round-cell tumors. *Semin Diagn Pathol* 2000;17:216–24.
27. Argani P, Perez-Ordóñez B, Xiao H, et al. Olfactory neuroblastoma is not related to the Ewing family of tumors: absence of EWS/FLI1 gene fusion and MIC2 expression. *Am J Surg Pathol* 1998;22:391–8.
28. Righi PD, Francis F, Aron BS, et al. Sinonasal undifferentiated carcinoma: a 10-year experience. *Am J Otolaryngol* 1996;17:167–71.
29. Rischin D, Porceddu S, Peters L, et al. Promising results with chemoradiation in patients with sinonasal undifferentiated carcinoma. *Head Neck* 2004;26:435–41.
30. Zong Y, Liu K, Zhong B, et al. Epstein–Barr virus infection of sinonasal lymphoepithelial carcinoma in Guangzhou. *Chin Med J (Engl)* 2001;114:132–6.
31. Tsang WYW, Chan JKC. Lymphoepithelial carcinoma. In: Barnes EL, Eveson JW, Reichart P, Sidransky D, editors. *Pathology and genetics of tumours of head and neck tumours*. (Kleihues P, Sobin LH, series editors. *World Health Organization classification of tumours*.) Lyon, France: IARC Press; 2005. p. 18.
32. Jeng YM, Sung MT, Fang CL, et al. Sinonasal undifferentiated carcinoma and nasopharyngeal-type undifferentiated carcinoma: two clinically, biologically, and histopathologically distinct entities. *Am J Surg Pathol* 2002;26:371–6.
33. Lopategui JR, Gaffey MJ, Frierson Jr. HF, et al. Detection of Epstein–Barr viral RNA in sinonasal undifferentiated carcinoma from Western and Asian patients. *Am J Surg Pathol* 1994;18:391–8.
34. Mills SE. Neuroectodermal neoplasms of the head and neck with emphasis on neuroendocrine carcinomas. *Mod Pathol* 2002;15:264–78.
35. Vasan NR, Medina JE, Canfield VA, et al. Sinonasal neuroendocrine carcinoma in association with SIADH. *Head Neck* 2004;26:89–93.
36. Rosenthal DI, Barker Jr. JL, el Naggar AK, et al. Sinonasal malignancies with neuroendocrine differentiation: patterns of failure according to histologic phenotype. *Cancer* 2004;101:2567–73.
37. Noguchi K, Urade M, Kishimoto H, et al. Establishment of a new cell line with neuronal differentiation derived from small cell neuroendocrine carcinoma of the maxillary sinus. *Oncology* 2004;66:234–43.
38. Perez-Ordóñez B, Caruana SM, Huvos AG, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. *Hum Pathol* 1998;29:826–32.
39. Georgiou AF, Walker DM, Collins AP, et al. Primary small cell undifferentiated (neuroendocrine) carcinoma of the maxillary sinus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;98:572–8.
40. Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. *Cancer* 1997;79:1729–36.
41. Watanabe K, Ogura G, Suzuki T. Intra-epithelial neuroendocrine carcinoma of the nasal cavity. *Pathol Int* 2003;53:396–400.
42. Ordóñez NG. Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. *Am J Surg Pathol* 2000;24:1217–23.
43. Galera-Ruiz H, Villar-Rodríguez JL, Sanchez-Calzado JA, et al. Sinonasal neuroendocrine carcinoma presenting as a nasopharyngeal mass. *Otolaryngol Head Neck Surg* 2001;124:475–6.