Chapter 2

Nasal Cavity and Paranasal Sinuses

2

A. Cardesa · L. Alos · A. Franchi

Contents

2.1 Introduction

2.1.1 Embryology

The midface, or area between the upper lip and forehead, develops at between 4 and 8 weeks' gestation [219]. The frontal prominence forms during the 4th postovulatory week and gives rise to the superior and middle portions of the face. The maxillary and nasal swellings form beneath the frontal prominence. At the end of the 4th week surface thickening of the nasal swellings forms the nasal placodes, which are of ectodermal origin and give rise to the epithelial lining of the nasal cavity and paranasal sinuses. The placodes invaginate, producing the nasal pits that become the anterior choanae (nostrils) and, less superficially, the primitive posterior choanae. The medial nasal and frontal processes give rise to the nasal septum, frontal bones, nasal bones, ethmoid sinus complexes and upper incisors. The lateral nasal and maxillary processes fuse to form the philtrum and columella. The cartilaginous nasal capsule forms deep to the nasal and frontal bones from the chondrocranium (skull base) during the 7th and 8th postovulatory weeks. The paranasal sinuses develop from the lateral nasal walls at the 6th foetal week, and their growth continues after birth, throughout childhood and adolescence.

2.1.2 Anatomy

The nasal cavities are separated by the nasal septum, and limited by a roof, which is formed by the cribriform plate of the ethmoid, and a floor, which is formed by the hard palate [261]. The lateral walls have three turbinates or conchae, and three horizontal spaces, or meatus, on each side. The nasolacrimal duct opens in the inferior meatus, whereas the middle meatus receives drainage from the frontal, anterior ethmoid and maxillary sinuses. Below the superior turbinate is the sphenoethmoid recess, with the openings of the sphenoid and posterior ethmoid sinuses. Each nasal cavity communicates posteriorly with the nasopharynx through the choanae. The paranasal sinuses are a group of cavities within the corresponding craniofacial bones (maxilla, sphenoid, ethmoid and frontal) that communicate with the nasal cavities through an ostium.

2.1.3 Histology

The nasal vestibule and skin share a similar histology. At the level of the limen nasi, the keratinising squamous epithelium gradually changes first to cuboidal or columnar epithelium, and then to ciliated respiratory-type epithelium, which lines most of the nasal cavity and all the paranasal sinuses, with the exception of the roof [261]. Numerous goblet cells are interspersed in the respiratory-type epithelium. The lamina propria contains several seromucous glands, lymphocytes, monocytes, and a well-developed vascular network, particularly evident in the inferior and middle turbinate. The olfactory epithelium is predominantly made of columnar non-ciliated sustentacular cells, with scattered bipolar sensory neurons and basal cells.

2.2 Acute and Chronic Rhinosinusitis

2.2.1 Viral Infections (Common Cold)

Infectious rhinitis is typically viral and is often referred to as the "common cold". It is more common in children than in adults, and the most frequently identified agents are rhinovirus, myxovirus, coronavirus and adenovirus [67, 271]. Swelling of the mucosa may cause obstruction of a sinus ostium, with subsequent secondary bacterial infection (acute bacterial sinusitis). The histologic findings include marked oedema and a non-specific mixed inflammatory infiltrate of the lamina propria.

2.2.2 Bacterial Infections

Bacterial rhinosinusitis usually follows a viral infection or allergic rhinitis, and the most commonly involved agents are Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis [11, 34]. A dense inflammatory infiltrate mainly made of neutrophils occupies the lamina propria. Acute bacterial rhinosinusitis usually resolves with antibiotic therapy. Complications are rare and include contiguous infectious involvement of the orbit or central nervous system.

2.2.3 Allergic Rhinitis

Allergic rhinitis (hay fever) is part of an inherited syndrome, which may also manifest as atopic eczema and asthma. In allergic rhinitis, airborne particles, such as grass pollens, moulds and animal allergens, are deposited on the nasal mucosa giving rise to acute and chronic reactions. Allergens combine with the IgE antibodies produced by the plasma cells of the nasal mucosa, which are avidly bound to the Fc-epsilon receptors on mast cells. This triggers degranulation of mast cells and releases the inflammatory mediators of the type I hypersensitivity reaction, causing rhinorrhoea and nasal obstruction. Microscopically, the nasal mucosa shows numerous eosinophils, abundant plasma and in some cases an increased number of mast cells. There is goblet cell

hyperplasia of the respiratory epithelium and the basement membrane, which is destroyed in the acute phase, appears considerably thickened in the chronic phase.

2.2.4 Atrophic Rhinitis

Atrophic rhinitis is a chronic inflammation of the nasal mucosa of unknown aetiology characterised by progressive nasal mucosal atrophy and by a thick, dense secretion, with a foetid smell and crusting [178]. Multiple factors may be involved in the pathogenesis, including chronic bacterial infections and nutritional deficiencies. Its incidence has markedly decreased in the last century, and nowadays most cases are secondary to trauma, surgery, granulomatous diseases, infection and radiation exposure [178]. Histologically, there is non-specific chronic inflammatory infiltrate, squamous metaplasia of the surface epithelium and of glandular excretory ducts, and atrophy of mucoserous glands [1, 69].

2.2.5 Hypertrophic Rhinitis

This term is applied to a condition of unknown aetiology, characterised by thickening of the sinonasal mucosa resulting from chronic inflammatory diseases [28, 71]. Frequently, these patients have undergone several sinus operations, each time with limited success and subsequent recurrence. Recurrent nasal polyposis is often associated.

2.2.6 Non-Suppurative Chronic Sinusitis

Chronic sinusitis is a complex, multifactorial disorder resulting from persistent acute inflammation or repeated episodes of acute or subacute sinusitis. There are usually predisposing factors like small sinus ostia, repeated episodes of common cold, allergy or acute sinusitis determining obstruction of the sinus ostia, reduction of ciliary activity (immotile cilia syndrome) and cystic fibrosis. The mucosal changes observed are variable and include basement membrane thickening, goblet cell hyperplasia, oedema of varying extent, inflammation (mostly lymphocytes and plasma cells) and polypoid change of the mucosa [242].

2.3 Sinonasal Polyps

2.3.1 Allergic Polyposis

Allergic sinonasal polyps consist largely of myxoid oedematous tissue with pseudocysts containing eosinophilic proteinaceous fluid and infiltrates of inflammatory cells [115]. They are covered by respiratory epithelium with variable ulceration, goblet cell hyperplasia, squamous metaplasia and thickening of the basement membranes. Seromucous glands and mucin-containing cysts may also occur. They arise most frequently in the ethmoidal region and the upper part of the nasal cavity. Allergic polyps usually exhibit heavy infiltration by eosinophils (Fig. 2.1a), marked thickening of the basement membranes and goblet cell hyperplasia. Most sinonasal polyps are of allergic origin. Epithelial dysplasia is present in a few cases. Granulomas may be present in polyps treated with intranasal injection, application of steroids or other oily medications. Atypical fibroblasts with abundant cytoplasm, poorly defined cell borders and large pleomorphic nuclei are present in a small proportion of cases [183]. These atypical cells occur individually and are more frequently found close to blood vessels (Fig. 2.1b) or near the epithelial surface. Such stromal atypia is a reactive phenomenon and it should not be confused with sarcoma.

2.3.2 Polyposis in Mucoviscidosis

Nasal polyps in mucoviscidosis show cystic glands filled with inspissated mucoid material and thickening of the basement membranes that surround the glands [22, 189]. Some other polyps are of infective or chemical aetiology. The histological appearances of nasal polyps do not always correlate well with their aetiology.

2.3.3 Polyposis in Immotile Cilia Syndrome and Kartagener's Syndrome

Immobile cilia syndrome (or primary ciliary dyskinesia) is a genetic disease affecting ciliary movement and resulting in respiratory infections and male infertility. Situs inversus may be associated (Kartagener's syndrome). About 15% of patients develop nasal polyps histologically indistinguishable from other nasal polyps. Ultrastructural analysis of nasal biopsies is needed to identify the alterations in the architecture of the cilium [177].

2.3.4 Antrochoanal Polyps

Antrochoanal polyps are polyps that arise in the maxillary antrum and extend into the middle meatus projecting posteriorly through the ipsilateral choana [106]. Antrochoanal polyps typically have prominent fibrous stroma surrounding thick-walled blood vessels

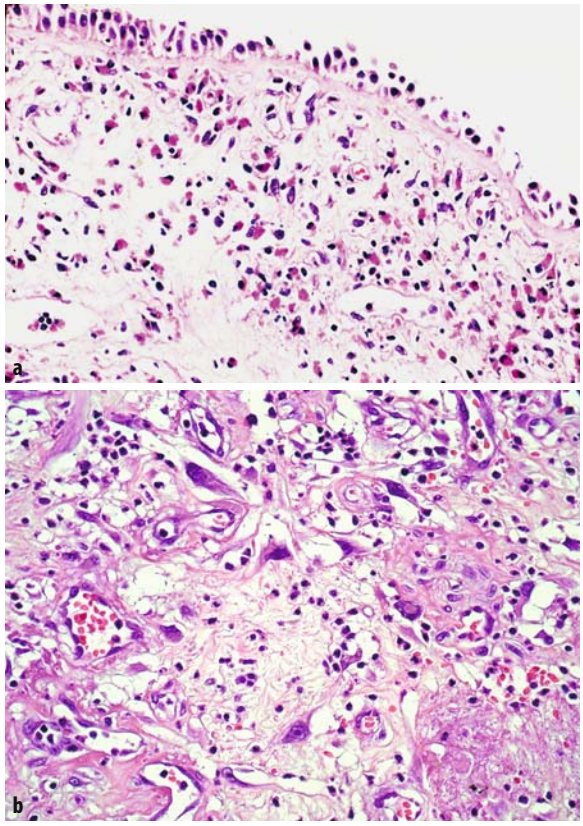

Fig. 2.1. **a** Allergic polyp with marked oedema of the stroma and heavy infiltration by eosinophils. **b** Atypical fibroblasts in an inflammatory allergic polyp: enlarged fibroblasts with bizarre nuclei and occasional prominent nucleoli appear interspersed in granulation tissue

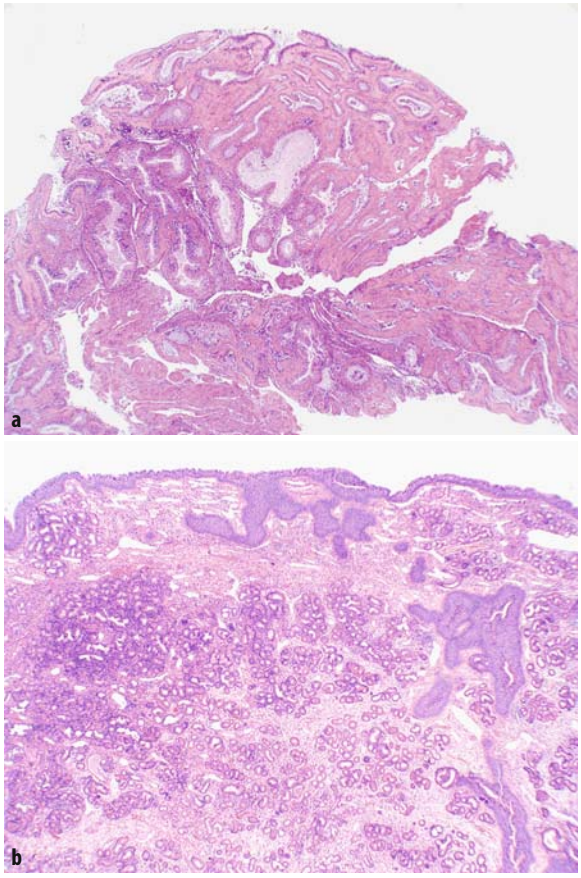

Fig. 2.2 **a** Respiratory epithelial adenomatoid hamartoma: glandular-like spaces lined by respiratory epithelium and supported by fibrous stroma. **b** Glandular hamartoma: abundant nodular aggregates of modified seromucous glands supported by slightly oedematous stroma

[7]. In addition, scattered, enlarged, stromal cells with hyperchromatic nuclei are not an uncommon finding in this type of polyp [235]. Those polyps that arise in the maxillary antrum and extend into the middle meatus projecting anteriorly are known as antronasal polyps.

2.4 Sinonasal Hamartomatous and Teratoid Lesions

2.4.1 Hamartomas

Sinonasal hamartomas are benign polypoid lesions in which well-developed branching glands and/or stroma with variable participation of different mesenchymal components are present [266]. These lesions may result from an exuberant hyperplastic reaction within the context of an inflammatory polyp. When the glands are mainly covered by ciliated respiratory epithelium the lesion is termed "respiratory epithelial adenomatoid hamartoma" (Fig. 2.2a). If the glandular component consists of seromucous glands they are known as "glandular hamartomas" (Fig. 2.2b). "Mesenchymal hamartomas" show predominance of skeletal muscle or of other mesenchymal elements.

2.4.2 Teratoid Lesions

Dermoid cysts of the nose constitute 5.5–12% of those of the head and neck region. More than half are detected in children 6 years old or less, and approximately a third are present at birth. They occur most commonly in the bridge of the nose and always in the midline [33, 63, 88, 254, 278]. Dermoid cysts are lined with mature keratinising squamous epithelium and contain appendages of the skin in the cyst wall, but no endoderm. The lumen is filled with cheesy, yellow-white material.

This lesion is differentiated from the very rare sinonasal teratoma by the limited variety of tissue types and the absence of endodermal components [100]. Epidermal inclusion cysts do not contain adnexa. Dermoid cysts of the nose should also be distinguished from encephalocele. We are unaware of hairy polyps occurring in the nose.

2.5 Pseudotumours

2.5.1 Mucocele

Mucocele is a cyst filled with mucus that develops within a sinus cavity as the result of occlusion of the ostium. Most commonly it is due to infection, but may also result from trauma or be congenital [109]. Retained secretions cause expansion of the sinus and bone erosion. The most common sites of occurrence are the frontal and the sphenoidal sinuses. The cyst is lined by respiratory epithelium that shows prominent goblet-cell hyperplasia [158, 184]. Expansion of the cyst may cause atrophy and metaplasia of the epithelium.

2.5.2 Organising Haematoma

Organising haematoma, also known as "cholesterol granuloma" or "rhinitis caseosa", is in most cases the result of occult submucosal haemorrhage in the maxillary sinus due to external trauma or tooth extraction [147]. Resolution of the haematoma produces the formation of cholesterol granulomas and fibrosis, simulating a foreign body reaction.

2.5.3 Amyloidosis

Isolated amyloid deposition in the sinonasal mucosa is a rare event, with about 20 cases reported in the English-language literature [180, 258]. Grossly, the lesion appears as a friable tumour-like mass, with a tendency to bleed. Histologically, there is a deposition of intensely eosinophilic material in the stroma, around blood vessels and around ducts of the mucoserous glands, which is often associated with diffuse chronic inflammation and foreign body granulomatous reaction. Amyloid stains orange with Congo red, and showed apple green birefringence under polarised light examination. Immunohistochemistry may help to identify the type of amyloid deposition.

2.5.4 Myospherulosis

Myospherulosis is characterised by the presence of cyst-like spaces lined by flattened histiocytes and containing clusters of brownish spherules resembling fungi [198, 217, 230]. They lie loosely or within sacs formed by thin refractile membranes. The brownish spherules do not stain with PAS or Gomori methanamine silver and their morphology does not correspond to any known fungus [228]. They are found within fibrous granulation tissue, which may show a foreign body reaction. The lesion is usually found in patients who have had previous operations [145]. It is now recognised that the spherules are extravasated red cells that have been altered by interaction with traumatised fat or petrolatum-based ointments and gauzes used in surgical procedures.

2.5.5 Eosinophilic Angiocentric Fibrosis

Eosinophilic angiocentric fibrosis is a rare, chronic, benign, idiopathic condition of the upper respiratory tract occurring predominantly in adult women [214, 248]. Initially, the histologic picture is characterised by non-necrotising eosinophilic vasculitis involving capillaries and venules of the sinonasal mucosa, accompanied by an inflammatory infiltrate with lymphocytes, plasma cells, histiocytes and occasional neutrophils [214]. In late lesions there is a characteristic obliterative perivascular onion-skin fibrosis, while the inflammatory infiltrate is less dense and eosinophils predominate [214]. The differential diagnosis includes reactive processes of the sinonasal mucosa, like Wegener's granulomatosis, Churg-Strauss syndrome, Kimura disease, and angiolymphoid hyperplasia with eosinophilia.

2.5.6 Heterotopic Brain Tissue

This lesion mostly occurs in young children, usually the result of a congenital abnormality related to a variant of meningoencephalocele [136, 196]. Commonly used synonyms are glial heterotopia and nasal glioma, although the latter is a misnomer. The lesion mainly arises at the base of the nose or in the upper part of the nasal cavity, and grossly may be polypoid. Histologically, it is mostly composed of a mixture of astrocytes, glial fibres and fibrous connective tissue. Multinucleated glial cells are frequently found. Some glial cells can have large nuclei resembling nerve cells. Immunostaining for glial fibrillary acidic protein is a helpful diagnostic adjunct. A few true nerve cells or even ependymal elements can rarely be identified. Mitoses are not found.

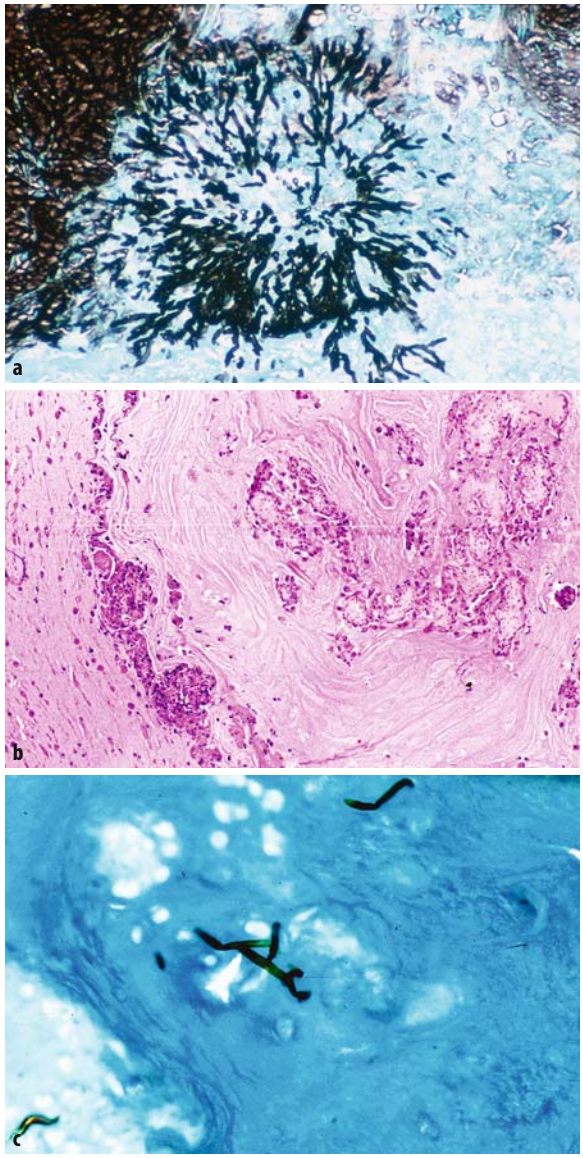

Fig. 2.3. **a** Sinonasal aspergilloma: densely packed branching hyphae of aspergillus forming a fungal ball. (Gomori's methenamine silver). **b** Sinonasal allergic mucinosis: dense aggregates of eosinophilic leukocytes distributed between pools of mucin. At the centre, one Charcot-Leyden crystal. **c** Allergic fungal sinusitis: scarce fungal hyphae found after diligent search in a lake of mucin (Gomori's methenamine silver)

2.6 Fungal Diseases

2.6.1 Aspergillosis

Aspergillosis is caused by *Aspergillus fumigatus*, *Aspergillus niger* and other species. In sections stained with PAS or Gomori methanamine silver the fungi appear as dichotomously branching septate hyphae 6–8 µm wide. Aspergillosis may occur as a non-invasive disease in which a mass of fungal hyphae (fungal ball) is present in a sinus (Fig. 2.3a). Invasive aspergillosis is seen more often in immunocompromised patients, associated with destructive inflammation of the sinonasal tissues [223]. The disease may also occur as an allergic mucinous sinusitis in which the sinuses contain masses of inspissated mucus with abundant eosinophils, Charcot-Leyden crystals (Fig. 2.3b), necrotic cell debris and scarce fungal hyphae (Fig. 2.3c) [137, 172]. The sinus mucosa shows inflammatory changes without fungal invasion.

2.6.2 Mucormycosis

Mucormycosis is caused by fungi of the class *Zygomycetes* and order *Mucorales* [73]. The most common species causing sinonasal infection are *Rhizopus arrhizus* and *Rhizopus oryzae*. In sections stained with PAS or Gomori methanamine silver the fungi are seen as non-septate hyphae measuring 10- to 20-µm wide, usually branching at right angles. Infection is usually opportunistic and causes rapidly progressive disease in poorly controlled diabetics and immunocompromised patients. The fungus has a tendency to invade blood vessels causing thrombosis; the affected tissues may exhibit coagulative necrosis and haemorrhage.

2.6.3 Rhinosporidiosis

Rhinosporidiosis is caused by the endosporulating fungus *Rhinosporidium seeberi*. The lesions are polypoid and occur principally in the nasal cavity [21, 161]. They are characterised by the presence of thick-walled sporangia measuring 50–350 µm in diameter and containing numerous mucicarminophilic spores. They are associated with a heavy chronic inflammatory reaction with occasional foci of suppuration and foreign body giant cell reaction.

2.7 HIV-Related Infections

Sinonasal infections are frequently observed in HIV patients, are often asymptomatic and tend to be recurrent or refractory [281]. They are due to various pathogens including cytomegalovirus [164], *Staphylococcus aureus*, fungi (*Aspergillus*) [170] and parasites (*Microsporidium*, *Cryptosporidium*) [66].

2.8 Mid-Facial Necrotising Granulomatous Lesions

2.8.1 Wegener's Granulomatosis

Wegener's granulomatosis is an immunologically mediated inflammatory disease characterised by granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis. Variable degrees of disseminated vasculitis involving both small arteries and veins may also occur. The lesions in the upper respiratory tract are ulcerative and destructive and occur mainly in the nasal cavity and paranasal sinuses. The hallmarks of Wegener's granulomatosis are the presence of geographic necrosis surrounded by palisaded histiocytes, granulomas and scattered giant cells, vasculitis with fibrinoid necrosis or infiltration of vessel walls by inflammatory cells, neutrophilic microabscesses and a mixed inflammatory infiltrate with variable fibrosis [57, 165]. Stains for acid fast bacilli and fungi are negative. There is no cytological atypia. The classic histological features of Wegener granulomatosis are not present in many biopsy specimens. Repeat biopsies and clinical correlations are often essential for early diagnosis. The disease may be restricted to the upper respiratory tract in the early stages. A high percentage of patients develop c-ANCA. More details are to be found in Chap. 3.

2.8.2 Lepromatous Leprosy

Lepromatous leprosy is the most frequent form of this type of disease involving the nasal cavity [101]. It is characterised by nodular masses of foamy macrophages (lepra cells) in which large numbers of acid fast bacilli (*Mycobacterium leprae*) are demonstrable by the modified Ziehl-Neelsen method. Tuberculoid leprosy is characterised by non-caseating granulomas and the indeterminate variant by a non-specific chronic inflammatory reaction; acid fast bacilli are seldom demonstrable in these types.

2.8.3 Tuberculosis

Tuberculosis of head and neck occurs infrequently and involvement of the nose is rare, representing in most cases a secondary event to pulmonary involvement [231]. In most cases there is a polyp of the nasal septum or an ulcerated granular lesion. Presence of intracranial extension may lead to a clinical diagnosis of malignancy [19]. Microscopically, there are caseating giant cell granulomas in which acid-fast bacilli may occasionally be identified. The definitive diagnosis is made by isolating *Mycobacterium tuberculosis* from tissue removed during biopsy.

2.8.4 Sarcoidosis

Sarcoidosis is a chronic multisystem granulomatous disorder that has a predilection for pulmonary and upper respiratory tract mucosa. The sinonasal mucosa is rarely involved, and most patients have generalised disease [143]. Discrete non-caseating granulomata composed predominantly of epithelioid histiocytes with multinucleated giant cells and a peripheral rim of lymphocytes are present in the mucosa. Stains for acid-fast bacilli are negative. The differential diagnosis includes other granulomatous disorders, like tuberculosis, leprosy, Wegener's granulomatosis and cholesterol granuloma [57].

2.8.5 Rhinoscleroma

Rhinoscleroma is caused by *Klebsiella rhinoscleromatis* [21], a capsulated gram-negative bacillus. Large nodular tumour-like masses are found in the nasal cavity and less often in other parts of the upper respiratory tract. They contain large macrophages with abundant clear or vacuolated cytoplasm (Mikulicz cells). The causative organism may be identified by the Warthin-Starry staining method or by immunostaining for the Klebsiella capsular antigen. There is heavy infiltration by chronic inflammatory cells, mainly plasma cells showing numerous Russell bodies.

2.8.6 Leishmaniasis

Leishmaniasis of the nasal region, when seen in Mediterranean countries, is mostly in the form of an "oriental sore" caused by *Leishmania tropica*. In Central and South America it is mostly seen in the form of mucocutaneous leishmaniasis caused by *Leishmania braziliensis* [153, 197]. The protozoan parasite is seen in the cytoplasm of histiocytes or extracellularly, measures 1.5–3.0 μm in its maximum dimension and has a nucleus and a rod-shaped kinetoplast that stains positively with Giemsa. The kinetoplast is more readily identified in Giemsa-stained smears of exudates or scrapings than in paraffin sections. The lesions, commonly found in the nasal mucosa and facial skin, are associated with chronic inflammatory reaction and granuloma formation. They are in general circumscribed and self-involutive in the case of the "oriental sore" and markedly destructive in mucocutaneous leishmaniasis.

2.8.7 Cocaine Abuse

Cocaine abuse may be associated with severe nasal necrotising inflammation [225]. Endoscopically, there is atrophy of the inferior and middle turbinates and ulceration of the nasal septum. Histologically, areas of acute and chronic inflammation are found; however, vasculitis is minimal or absent and granulomas may be present. The lesion may be confused with Wegener's granulomatosis.

2.8.8 Local Steroid Injections

A granulomatous lesion of the nasal mucous membranes has been observed in patients treated with injections of steroid preparations [272]. There is a central deposition of amorphous material bordered by histiocytes and foreign body giant cells. Occasional particles of birefringent crystalline material may be present. Special stains should be performed to exclude the presence of micro-organisms.

2.9 Benign Epithelial Neoplasms

2.9.1 Sinonasal Papillomas

Sinonasal papillomas may be divided into squamous cell papillomas of the nasal vestibule and schneiderian papillomas of the nasal cavity and paranasal sinuses [121]. The first are covered by epithelium of the skin surface. The latter are lined by well-differentiated respiratory epithelium (referred to as the schneiderian membrane) and comprise three histopathological types: exophytic, inverted and oncocytic. The histopathological features that clearly differentiate between the three types of schneiderian papillomas have been well documented [173]. Human papilloma virus (HPV) types 6 and 11 are involved in the pathogenesis of exophytic papillomas, but not in the other two variants of schneiderian papillomas [35, 89, 128]. All oncocytic papillomas examined have been HPV-negative [35, 128, 221].

2.9.1.1 Squamous Cell Papilloma

ICD-O:8052/0

Squamous cell papillomas are located in the nasal vestibule and are formed by keratinising stratified squamous epithelium of the skin surface [122]. They are exophytic and consist of a thickened layer of differentiated squamous epithelium, without evidence of atypia or mitoses, which is supported by arborescent stalks of fibrovascular stroma. Varying degrees of keratinisation are present and either hyperkeratosis, parakeratosis or both may be seen. They are benign, rarely recur after simple excision. Its main differential diagnosis is the exophytic schneiderian papilloma.

2.9.1.2 Exophytic Papilloma

ICD-O:8121/0

Exophytic papilloma, also known as "everted" or "fungiform" papilloma, is a single, warty tumour measuring up to 1.5 cm in diameter, arising most frequently at the nasal septum and only very rarely in the lateral nasal walls or in paranasal sinuses [122]. Males are predominantly affected. Patients tend to be younger than with other types of schneiderian papilloma. Exophytic papillomas are almost always unilateral [54]. No side is preferred and bilaterality is exceptional. The tumour is composed of branching papillary structures, with papillae covered by stratified non-keratinising squamous epithelium, admixed with intermediate or transitional cells and with ciliated respiratory epithelium that contains interspersed mucin-secreting cells. Koilocytosis is not infrequently found in the squamous epithelium. Seromucinous glands are abundantly found when the underlying submucosa is removed.

The two main differential diagnoses are inverted papilloma and oncocytic papilloma. Neither the invaginated pattern of growth of inverted papillomas nor the oncocytic columnar epithelium of oncocytic papillomas are found in exophytic papillomas [173]. Cylindrical cell carcinoma can be easily ruled out by the lack of atypia and invasion. Wide surgical excision is the best choice of treatment to avoid recurrences. Recurrences occur in about 20–40% of cases, which is less than in inverted papillomas. Malignant transformation almost never occurs in exophytic papillomas.

2.9.1.3 Inverted Papilloma

ICD-O:8121/0

Inverted papilloma is the most common type of schneiderian papilloma. This lesion occurs almost exclusively in the lateral wall of the nasal cavity and in the paranasal sinuses, although on rare occasions it may also arise on the nasal septum [226]. Grossly, they frequently have a polypoid appearance, but they differ from nasal polyps of the common type by their histological features. Inverted papillomas are composed of invaginating crypts, cords and nests covered by non-keratinising squamous epithelium, which alternates with columnar ciliated respiratory epithelium and with intermediate or transitional epithelium (Fig. 2.4a). This newly formed duct system is similar to the embryonic development of the nasal mucosa [240]. The multilayered epithelium typically contains mucous cells and mucin-filled micro-

cysts. The invagination of the mucosa may result in the presence of apparently discontinuous cell masses lying deep to the epithelial surface, but the basement membrane is intact and may be shown in continuity with that of the surface epithelium [226]. An inverted growth is the hallmark of inverted papilloma, but varying degrees of papillary growth may be seen at the surface [54]. The surface is characteristically lined by a respiratory type of epithelium; nevertheless, foci of surface keratinisation are occasionally present [122]. A few regular mitoses may be found in the basal and parabasal layers. Although the nuclei may show mild nuclear irregularities and hyperchromatism, no disturbances of the cellular polarity are found. An abundant and oedematous connective tissue stroma is a common feature of inverted papillomas. It usually contains macrophages and neutrophils, but eosinophils may also be present. This inflammatory infiltrate may also be present between the epithelial cells, within the dilated lumens of invaginated crypts, and within the numerous microcysts that usually occur in the respiratory epithelium. Seromucinous glands are absent, but branching gland ducts are often present. The tumour grows by extension to involve the contiguous sinonasal epithelium.

If treated only by local surgical excision, recurrence occurs in up 75% of cases. Therefore, lateral rhinotomy and medial maxillectomy are advisable for tumours of the lateral nasal wall [236]. Carcinoma develops in about 10–15% of inverted papillomas [122, 211, 236]. Carcinoma may coexist with inverted papilloma at the initial presentation or originate subsequently [122, 273]. According to the experience of Michaels and Hellquist [171], carcinoma does not usually develop in the course of recurrences of inverted papilloma. In the presence of severe atypia or marked keratinisation in an inverted papilloma malignant transformation is always suspected (Fig. 2.4b). In these instances the entire specimen should be thoroughly examined to exclude an associated carcinoma. Most associated carcinomas are squamous [204], although other types may also occur such as verrucous carcinoma [192].

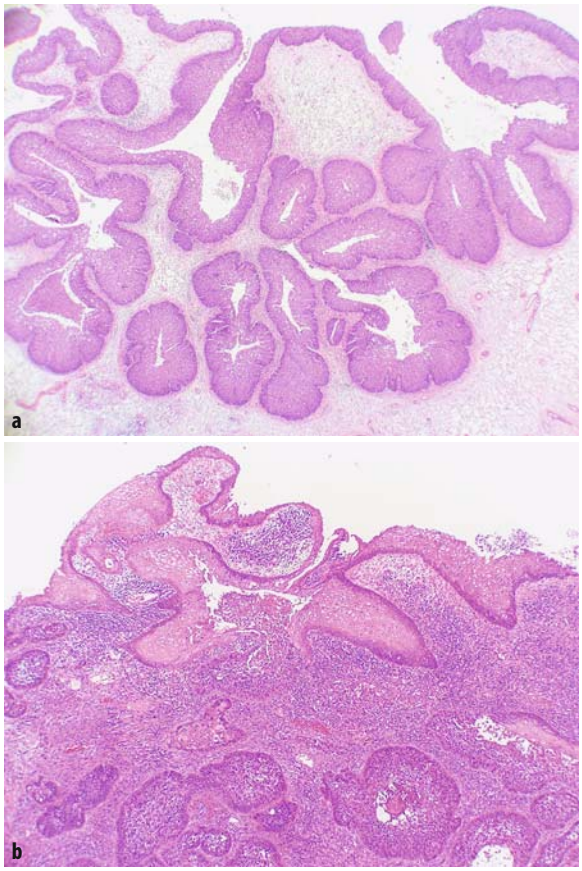

Fig. 2.4. **a** Inverted papilloma: prominent invaginating crypts lined by hyperplastic respiratory epithelium are supported by oedematous connective tissue. **b** Squamous cell carcinoma ex inverted papilloma: remnants of benign invaginating crypts are seen between invasive cords of squamous epithelium

2.9.1.4 Oncocytic Papilloma

ICD-O:8121/1

Oncocytic papilloma, also known as "columnar" or "cylindric" cell papilloma [226], is the least common type of schneiderian papilloma. It constitutes less than 5% of all sinonasal papillomas [18, 122, 173, 262]. Both sexes are equally affected. Bilaterality has not been documented. Tumours are in general small, although occasionally may reach various centimetre measurements in their greatest dimension. They are composed of exophytic fronds and endophytic invaginations lined by pseudostratified or multilayered columnar cells with prominent oncocytic features. The cells have uniform hyperchromatic nuclei and abundant eosinophilic, occasionally granular, cytoplasm that contains abundant mitochondria and stains for the mitochondrial enzyme cytochrome C oxidase [59]. Goblet cells are not found. Cilia may be occasionally encountered on the superficial epithelial layer. Intraepithelial microcysts containing mucin and neutrophils are usually present. These microcysts are larger than the similar structures also seen in inverted papilloma. The tumour resembles inverted papilloma in its sites of occurrence, the lateral wall of the nasal cavity and the maxillary antrum. The rate of recurrence is considered to be 36%, which is lower than in inverted papilloma. The low frequency of this tumour makes it difficult to evaluate its true malignant potential, which seems to be similar to that of inverted papilloma [262]. Atypical hyperplasia and carcinoma in situ changes can be occasionally found (Fig. 2.5). Surgical excision with wide margins is the treatment of choice. Invasive squamous cell carcinoma, high-grade mucoepidermoid

carcinoma and undifferentiated carcinoma have been reported in association with oncocytic papilloma [18, 122, 135, 265, 274].

2.9.2 Salivary-Type Adenomas

Pleomorphic adenoma is the most frequent benign glandular tumour of the sinonasal region. Most arise on the nasal septum and the rest on the lateral nasal wall or turbinates. Origin in the maxillary antrum is rare. The recurrence rate of sinonasal pleomorphic adenoma is much lower than for its counterpart in the major salivary glands [56, 109]. Rare examples of sinonasal oncocytoma, myoepithelioma and basal cell adenoma have been reported [27, 55, 103, 277], as well as one case of sinonasal myoepithelioma transformed into myoepithelial carcinoma after various recurrences [9].

2.9.3 Pituitary Adenomas

The rare pituitary adenomas of the sinonasal region are in most instances extensions from intrasellar tumours. Very unusually, they arise from ectopic pituitary tissue as tumours from the sphenoid sinus or the nasal cavity. Histologically, they are similar to tumours within the sella [61, 151].

2.10 Benign Sinonasal Soft Tissue Neoplasms

2.10.1 Haemangiomas

Haemangiomas of the upper respiratory tract may be of the capillary, cavernous or venous types [90]. The most common type is the capillary haemangioma which consists of lobules of blood-filled capillaries separated by loose connective tissue. The lesion should be distinguished from granulation tissue and from the vascular ectasias found in Rendu-Weber-Osler disease.

2.10.2 Haemangiopericytoma (Glomangiopericytoma)

ICD-O:9150/1

Haemangiopericytoma is characterised by the proliferation of oval, polyhedral or spindle-shaped cells enmeshed by collagen type IV fibres and arranged around vascular channels that are lined by a single layer of endothelial cells. The tumour contains numerous thin-walled blood vessels and the tumour cells, typically arranged around the blood vessels, are of uniform size with regular oval

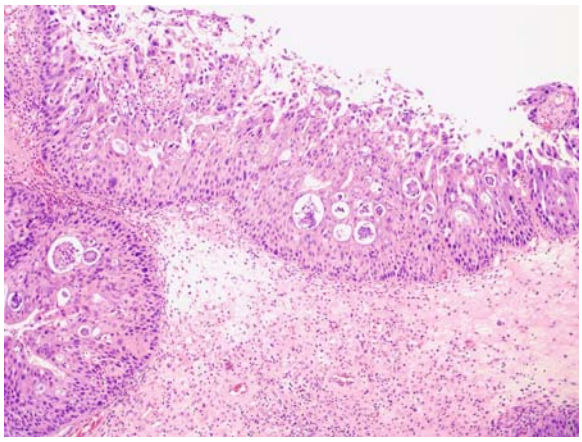

Fig. 2.5. Oncocytic papilloma with atypical cells: papillary stalks covered by columnar cells with frequent atypical nuclei and oncocytic cytoplasm-forming microcysts

or elongated nuclei and pale cytoplasm (Fig. 2.6). The cells may also be arranged in short, haphazard fascicles or in sheets of closely packed cells containing compressed capillaries. Areas of poor cellularity, myxoid change and fibrosis are not uncommon. The tumour cells are entirely situated outside the capillaries, which are lined by a single layer or normal-looking endothelium. This feature, well shown by reticulin staining or by anti-collagen IV antibodies, helps to distinguish the tumour from angiosarcoma. The distinction from other well-vascularised mesenchymal tumours is usually made by exclusion. Haemangiopericytomas of the nasal cavity are generally less aggressive than those occurring elsewhere. They exhibit a more orderly structure with minimal mitotic activity, but tend to recur after removal and may rarely metastasise [249]. Muscle-specific actin is focally positive in tumour cells. The term glomangiopericytoma has been recently proposed for this entity [267a].

2.10.3 Solitary Fibrous Tumour

ICD-O:8815/0

Solitary fibrous tumour of the nose, paranasal sinuses and nasopharynx is in most instances a benign fibroblastic proliferation with variable cellularity and vascularity (Fig. 2.7) having features identical to those of solitary fibrous tumour of the pleura [8, 168, 279]. Its main differential diagnoses are sinonasal haemangiopericytoma and nasopharyngeal angiofibroma.

2.10.4 Desmoid Fibromatosis

ICD-O:8821/1

Desmoid fibromatoses are a group of non-metastasising unencapsulated fibrous tissue proliferations that have a

tendency towards local invasion and recurrence, which rarely arise in the sinonasal mucosa [96]. They comprise interlacing fascicles of bland spindle-shaped fibroblasts, in a collagenous or myxoid background. The main differential diagnoses are fibrosarcoma and reactive fibrosis. Desmoid fibromatosis of the sinonasal tract shows lower recurrence rates than desmoid fibromatoses arising in other locations.

2.10.5 Fibrous Histiocytoma

ICD-O:8830/0

Benign fibrous histiocytoma presents as a yellow-tan nodule or polyp, most commonly causing nasal obstruction or bleeding [201]. It is composed of spindle-shaped cells producing a storiform pattern admixed with histiocytic cells and multinucleated giant cells. Distinction from other benign sinonasal spindle cell proliferations is largely based on the immunohistochemical findings. Benign fibrous histiocytomas may recur if incompletely excised.

2.10.6 Leiomyoma

ICD-O:8890/0

Sinonasal leiomyoma is a rare tumour occurring in adults, preferentially involving the nasal cavities, with non-specific symptoms of nasal obstruction [91]. Its morphologic and immunohistochemical profile is identical to that of leiomyomas of other sites. It has been postulated that they may originate from blood vessel walls. Distinction from sinonasal leiomyosarcoma is based on the absence of atypia and mitoses. Huang and Antonescu have proposed separating a category of smooth muscle tumours of uncertain malignant potential, characterised by the presence of 1–4 mitotic figures/10 high power fields, that tend to pursue a more aggressive behaviour than leiomyomas [119].

2.10.7 Schwannoma and Neurofibroma

ICD-O:9560/0, 9540/0

About 4% of schwannomas of the head and neck region arise in the sinonasal tract [202]. They usually present as polypoid lesions involving the nasal cavity and/or a paranasal sinus, with non-specific symptoms of obstruction, compression, or extension in the surrounding structures [202]. Histologically, the tumour is composed of elongated wavy-shaped monomorphic spindle cells, with eosinophilic cytoplasm and oval nucleus. Antoni type A and type B areas usually coexist within the lesion, and nuclear palisading may be present. Focal degenerative nuclear atypia has been described [108], while mitotic activity is absent to low. A consistently reported

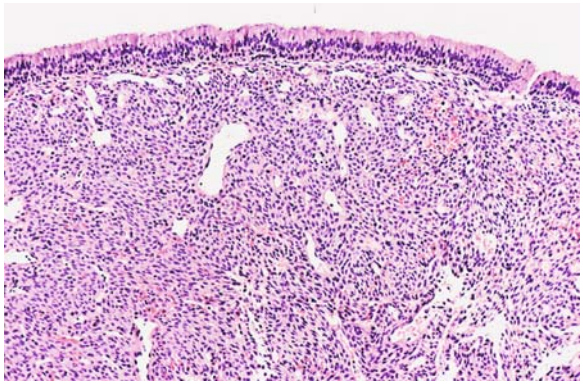

Fig. 2.6. Haemangiopericytoma: interconnected thin-walled blood vessels surrounded by uniform spindle-shaped cells with oval or elongated nuclei

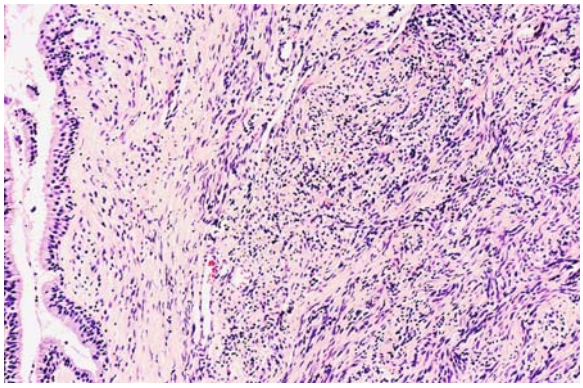

Fig. 2.7. Solitary fibrous tumour: fibroblastic proliferation, collagen production and dilated blood vessels. Identical features to the pleural counterpart

feature of sinonasal schwannomas is the lack of tumour encapsulation that determines an apparently infiltrative growth pattern [36, 108]. Immunohistochemically, sinonasal schwannoma is intensely reactive for S-100 protein [108]. The differential diagnosis includes other spindle cell lesions of the sinonasal mucosa, like juvenile angiofibroma, solitary fibrous tumour and leiomyoma. Particular care should be taken when evaluating cellular schwannomas with a predominance of Antoni type A areas, which should not be confused with malignant spindle cell neoplasms, like fibrosarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumour, and spindle cell melanoma.

Neurofibromas of the sinonasal mucosa are usually not associated with the Von Recklinghausen syndrome, and appear as unencapsulated lesions composed of a mixture of Schwann cells and fibroblasts embedded in a predominantly myxoid stroma [117, 202]. Due to the overlapping of the histologic features, it may be difficult to differ-

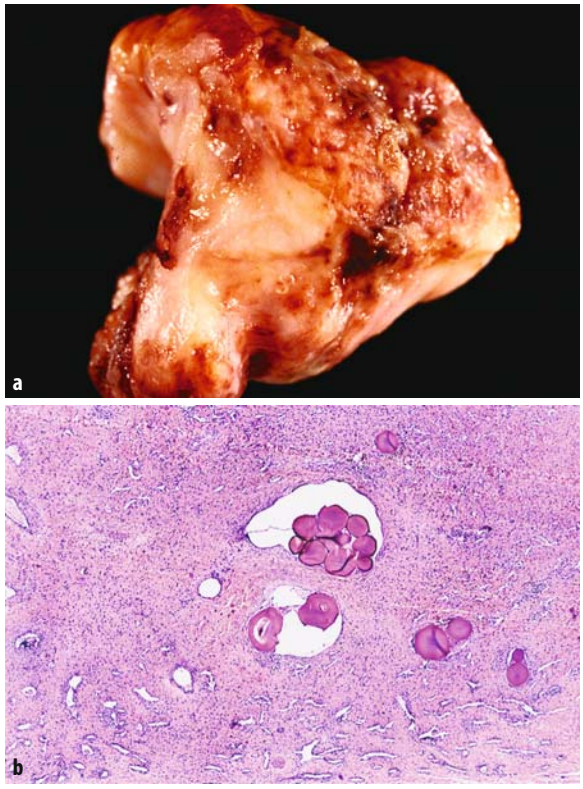

Fig. 2.8. Juvenile angiofibroma. **a** Polypoid mass of white-red cut surface and rubbery consistency. **b** Vascular elements embedded in fibrous tissue showing intravascular microembolisation, a treatment modality prior to surgery

entiate neurofibromas from schwannomas of the sinonasal mucosa. Neurofibromas should also be distinguished from myxomas, which are S-100 protein-negative.

2.10.8 Meningioma

ICD-O:9530/0

Meningiomas of the sinonasal tract may extend directly from the central nervous system or arise from ectopic extracranial tissue. Although always rare, they are more commonly seen in the orbit, ear and skin of the head and neck than in the sinonasal tract. Histologically, they are similar to meningiomas elsewhere, the meningothelial type being the most frequent. Sinonasal meningiomas tend to occur in younger patients than intracranial meningiomas [118, 203].

2.10.9 Paraganglioma

ICD-O:8680/1

There are few reports on nasal paragangliomas. The tumours originate in the middle turbinates and ethmoid sinuses. Histologically, they are similar to paragangliomas elsewhere [12, 98, 187].

2.10.10 Juvenile Angiofibroma

ICD-O:9160/0

Juvenile nasopharyngeal angiofibroma arises in the confluence of the posterolateral nasal wall and the lateral nasopharynx and occurs almost exclusively in males during adolescence [90, 125]. The tumour is sessile or polypoid (Fig. 2.8a) and is histologically benign, but has a tendency to recur and is locally destructive, causing pressure necrosis of adjacent soft tissue and bone. It may occasionally extend into paranasal sinuses, orbit and cranial fossae. It is composed of vascular and fibrous elements in varying proportions. The vessels in the superficial portions of the tumour are mainly gaping capillaries that may become compressed with increasing stromal fibrosis. Thick-walled vessels without elastic membranes and with irregular, incomplete or absent muscle coats and focal intimal thickenings are usually present in the deeper portions of the tumour. These vessels resemble those normally seen in the submucosa of the nasal conchae. The vascular elements are embedded in fibrous tissue, which varies in cellularity and collagenisation. Stellate fibroblast-like cells are often present close to the blood vessels. The fibroblastic cells of nasopharyngeal angiofibroma are strongly positive for testosterone receptors [120]. Ultrastructurally, the nuclei of angiofibroma contain characteristic dense granules [251]. Occasionally, the fibroblasts may exhibit cytologic atypia, and some of these cells may be multinucleated, but mitosis is rare. Mast cells may be numerous. There may be focal thrombosis, haemorrhage and chronic inflammatory reaction. With the advent of preoperative selective embolisation, iatrogenic emboli (Fig. 2.8b) are increasingly encountered in resected specimens [232]. For more details on this tumour see Chap. 6.

2.11 Malignant Sinonasal Tumours

Malignant sinonasal tumours represent less than 1% of all cancers seen in humans and about 3% of all malignancies of the head and neck region [160]. Despite the low rate of malignancy arising in the sinonasal tract, a great variety of histological types of tumours may be found [216, 226]. The use of electron microscopy and more recent advances in immunohistochemistry and molecular biology have made it possible to refine the criteria for their correct recognition.

Geographical differences in the relative frequency of certain histological types of malignant sinonasal tumours may be related to variations in the exposure

Table 2.1. Malignant sinonasal tumours at the Hospital Clinic, University of Barcelona Medical School

Histological type of tumour	Frequency n	%	Men n	%	Women n	%	Mean age	Age range
Squamous cell carcinoma	54	27	38	70	16	30	64	39–87
Undifferentiated carcinoma	26	13	19	73	7	27	60	41–87
Cylindrical cell carcinoma	19	9.5	15	79	4	21	59	26–84
Malignant lymphoma	19	9.5	15	79	4	21	59	9–89
Malignant melanoma	14	7	7	50	7	50	69	56–89
High-grade adenocarcinoma	13	7	10	77	3	23	59	16–81
Adenoid cystic carcinoma	11	5	7	64	4	36	58	22–69
Low-grade adenocarcinoma	10	5	4	40	6	60	64	28–92
Olfactory neuroblastoma	7	3	3	43	4	57	36	2–67
Mucoepidermoid carcinoma	4	2	3	75	1	25	55	50–61
Malignant fibrous histiocytoma	4	2	3	75	1	25	56	35–65
Plasmacytoma	4	2	3	75	1	25	51	50–65
Rhabdomyosarcoma	4	2	2	50	2	50	30	8–51
Malignant schwannoma	3	1.5	1	33	2	67	57	27–70
Adenosquamous carcinoma	2	1	2	100	–	–	66	61–71
Myoepithelial carcinoma	2	1	2	100	–	–	47	29–66
Kaposi's sarcoma	2	1	2	100	–	–	37	34–40
Teratocarcinosarcoma	1	0.5	1	100	–	–	76	–
Ewing's sarcoma (PNET)	1	0.5	–	–	1	100	23	–
Total	**200**	**100**	**137**	**69**	**63**	**31**	**58**	**2–92**

to environmental carcinogens (see epidemiological aspects Sect. 11.1.1). In Table 2.1 the histological types of malignant sinonasal tumours diagnosed at the Hospital Clinic of the University of Barcelona are presented in decreasing order of frequency. The most frequent histological types are: keratinising squamous cell carcinoma, undifferentiated carcinoma, cylindrical cell carcinoma, malignant lymphoma, malignant melanoma, intestinal-type adenocarcinoma, adenoid cystic carcinoma, low-grade adenocarcinomas and olfactory neuroblastoma.

A practical way to start classifying malignant sinonasal tumours is to separate them initially into large and small cell categories. Among the large cell malignant tumours the most common types are: squamous cell carcinoma, cylindrical cell carcinoma, malignant melanoma, intestinal-type adenocarcinoma, and low-grade adenocarcinomas. To the most common small cell tumours belong the sinonasal undifferentiated carcinoma, malignant lymphoma, adenoid cystic carcinoma and olfactory neuroblastoma. Large cell tumours account for approximately 75% of the malignant sinonasal tumours and the small cell tumours for the remaining 25% [41].

For staging of malignant sinonasal tumours the TNM classification of 2002 and the TNM atlas of 2004 are recommended, since nasal cavity tumours are now included [237, 271a].

2.11.1 Keratinising Squamous Cell Carcinoma

ICD-O:8071/3

At the nasal vestibule, keratinising squamous cell carcinoma is the most common malignancy [130, 167, 245]. Due to early recognition and easy access to treatment, they usually have a more favourable prognosis than their counterpart of the sinonasal region.

Sinonasal keratinising squamous cell carcinoma represents up to 45–50% of the malignant tumours of this region in several series [93, 259]. At the Hospital Clinic of the University of Barcelona, where non-keratinising squamous cell carcinomas (see Sect. 2.11.2 on cylindrical cell carcinomas) are grouped separately from keratinising squamous cell carcinomas, the latter account for only 27% of the sinonasal malignancies. They predominate in males and the great majority are seen in patients aged over 50 years. The maxillary antrum, the lateral nasal wall and the sphenoidal sinuses are the most common sites, whereas the frontal and sphenoid sinuses are rarely involved. These tumours grow by local extension, infiltrating the neighbouring structures, but lymph node metastases are rare [215]. For neoplasms circumscribed to the nasal cavity the 5-year survival is slightly above 50% [30], whereas in neoplasms of the maxillary antrum the 5-year survival may be as low as 25% [146].

The occupational epidemiology of sinonasal squamous cell carcinoma has been strongly related to exposure to nickel [141, 243, 252, 253] and to a lesser extent to chromium, isopropyl alcohol and radium [218]. As in other territories of the respiratory tract, a definite association between sinonasal squamous cell carcinoma and cigarette smoking has been documented [26, 146]. Chronic sinonasal inflammation is considered a predisposing factor. A case of carcinoma of the maxillary antrum after thorotrast exposure has been reported [97]. Nitrosamines and to a lesser extent formaldehyde are strong nasal carcinogens in laboratory rodents [44, 155].

Keratinising squamous cell carcinomas originate in the respiratory sinonasal mucosa from areas of pre-existing squamous metaplasia and manifest the same range of histological appearances as those arising in other sites. They are characterised by the proliferation of malignant epithelial cells with squamous differentiation and intercellular bridges. Malignancy is graded according to the degree of differentiation, cellular pleomorphism and mitotic activity. They are divided into well-differentiated, moderately differentiated and poorly differentiated forms. Well-differentiated carcinomas are uncommon in this territory and when encountered need to be differentiated from pseudoepitheliomatous types of hyperplasia and from verrucous carcinoma. Most conventional keratinising squamous cell carcinomas of the sinonasal tract present as moderately or poorly differentiated tumours. Special types, such as verrucous carcinoma [104], spindle cell carcinoma [205, 276], basaloid-squamous cell carcinoma [16, 269] and adenosquamous carcinoma [10, 94] are occasionally found in the sinonasal tract. Regional lymph node involvement is seen in about 17% of sinonasal squamous cell carcinomas and distant metastases in about 1.5% [215].

2.11.2 Cylindrical Cell Carcinoma

ICD-O:8121/3

Cylindrical cell carcinoma, also known as non-keratinising squamous cell carcinoma, transitional cell carcinoma or schneiderian carcinoma, is a tumour composed of malignant proliferating cells derived from sinonasal respiratory (schneiderian) epithelium. The name cylindrical cell carcinoma was first coined by Ringertz in 1938 [212] and recommended as the preferred term by Shanmugaratnam in the WHO classification of 1991 [226].

Grossly, the tumours grow in most cases as exophytic masses showing either a corrugated or a smooth surface. They may arise from the antrum, the lateral nasal wall or the ethmoid, the maxillary antrum being the most frequent site [193, 194]. They may occur concomitantly with other non-neoplastic polypoid formations. Microscopically, cylindrical cell carcinoma is composed of papillary fronds (Fig. 2.9a), thick ribbons and polystratified masses of cells that give rise quite often to invaginations of the surface epithelium, which at low magnification may mimic inverted papilloma. The tumour cells are commonly cylindrical and have a tendency to form palisade arrangements perpendicular to the underlying basement membrane (Fig. 2.9b). The nuclei are atypical and show increased mitotic activity, as well as abnormal mitotic figures. The pattern of invasion is usually expansive, being characterised by pushing margins with focal infiltration of the stroma. The basement membrane remains in most cases conspicuous, despite stromal infiltration, which should not be regarded as carcinoma in situ. Foci of squamous metaplasia, with transition from cylindrical to squamous epithelium, are not uncommon and when extensive these tumours may be indistinguishable from squamous cell carcinoma. This resulted in denominations such as "transitional cell carcinoma" and "non-keratinising squamous cell carcinoma", which may be confusing. The first because the term transitional has also been applied to carcinomas of the lymphoepithelial type, and the second due to the fact that tumours called "non-keratinising squamous cell carcinoma" also have foci of keratinisation [267a]. In addition, the term cylindrical cell carcinoma should be preferred to non-keratinising squamous cell carcinoma because "pure" cylindrical cell carcinomas, without any squamous cell component, carry a better prognosis than conventional squamous cell carcinomas [84]. Very recent observations suggest a strong etiologic relationship of cylindrical cell carcinoma to high-risk human papillomavirus [69a]. A high proportion of these tumours show marked immunoreactivity for p16.

More aggressive types of carcinoma, such as sinonasal undifferentiated carcinoma (SNUC) or high-grade adenocarcinoma, may appear occasionally intermingled with cylindrical cell carcinoma [226]. Two cases of cylindrical cell carcinoma with endodermal sinus-like features have been reported [162]. A full examination of the resected specimen is therefore mandatory before labelling a tumour a "pure cylindrical cell carcinoma".

The two main differential diagnoses of cylindrical cell carcinoma are the schneiderian papillomas of the inverted and oncocytic types, especially when they have concomitant carcinomatous changes. Both types of papilloma lack the atypical cellularity constantly seen in cylindrical cell carcinoma. When schneiderian papillomas coexist with cylindrical cell carcinomas, or with other types of carcinoma, the two components usually appear demarcated from one another although in contiguity. When the invaginating crypts of an inverted papilloma are filled with the cords and ribbons of a keratinising or non-keratinising squamous cell carcinoma, the lesion represents a conventional squamous cell carcinoma arising in an inverted papilloma, which implies a worse prognosis than that of cylindrical cell carcinoma.

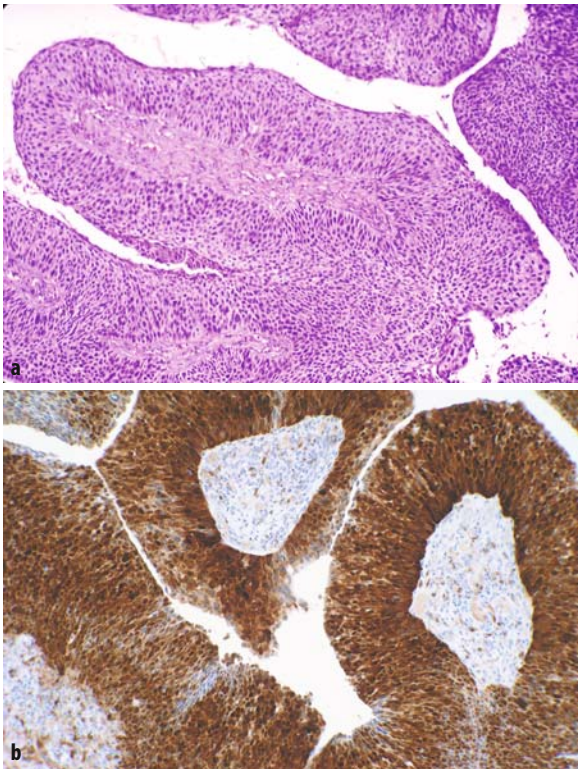

Fig. 2.9. Cylindrical cell carcinoma. **a** Papillary structures covered by malignant cells with cylindrical cytoplasm and basal nuclei arranged in palisades. **b** Marked immunoreactivity of the epithelial neoplastic cells for p16, which is related to high-risk HPV

2.11.3 Sinonasal Undifferentiated Carcinoma

ICD-O:8020/3

Sinonasal undifferentiated carcinoma (SNUC) is defined as a high-grade malignant epithelial neoplasm of the nasal cavity and paranasal sinuses, composed of small to medium-sized cells, lacking evidence of squamous or glandular differentiation and of rosette formation [48, 86, 114]. Cigarette smoking [86] and nickel exposure [252] have been associated with SNUC. Epstein-Barr virus (EBV) and the deletion of the retinoblastoma gene have been ruled out as factors involved in the development of this tumour [127]. Ionising radiation is another aetiologic factor, as radiotherapy either for retinoblastoma or for nasopharyngeal carcinoma has been associated with SNUC [127].

Sinonasal undifferentiated carcinoma occurs in both sexes over a wide age range, with a median in the 6th decade of life. It commonly originates from the ethmoidal region as a large fungating mass. Grossly, the tumours are quite frequently extensive lesions, obstructing the nasal cavity either unilaterally or bilaterally and invading the adjacent sinonasal structures (Fig. 2.10a), as well as the orbit, skull base and the brain. Microscopically, SNUC is composed of small to medium-sized, undifferentiated cells, which arise via dysplastic changes from the basal cells of the surface epithelium. The cells are polygonal with distinct borders, showing round to oval, hyperchromatic or vesicular nuclei, with either inconspicuous or slightly prominent nucleoli, surrounded by a moderate amount of either amphophilic or eosinophilic cytoplasm (Fig. 2.10b). Mitotic figures are common. The tumour forms nests, cords and sheets of cells that show frequent areas of central necrosis and tendency to vascular (Fig. 2.10c) and perineural invasion. Ultrastructural studies demonstrate poorly formed desmosomes in quite a number of cells, while the presence of tiny bundles of tonofilaments is very rare. Neurosecretory granules are very rarely found. SNUC are immunoreactive with epithelial markers, such as CAM 5.2 and epithelial membrane antigen (EMA). Variable reactivity can be seen with neuron-specific enolase (NSE), whereas there is negative reactivity for synaptophysin, chromogranin and other neuroendocrine markers. SNUC are also negative for EBV [48, 127].

The two main differential diagnoses of SNUC are small cell (neuroendocrine) carcinoma (SCC) and high-grade olfactory neuroblastoma (ONB). All three entities may share some clinical and light microscopic features. However, SNUC and SCC show a marked immunoreactivity for cytokeratins that is not seen in ONB, and SNUC lacks the neuroendocrine immunoreactivity seen in SCC and ONB. Most lesions categorised in the past as grade IV ONB are now considered to be either SNUC or SCC. This is important because SNUC and SCC have a worse prognosis than ONB. In addition, SNUC needs to be distinguished from other primary sinonasal tumours, such as solid adenoid cystic carcinoma, microcytic malignant melanoma, cylindrical cell carcinoma, primary sinonasal nasopharyngeal-type undifferentiated carcinoma, lymphoma and others (Table 2.2).

Sinonasal undifferentiated carcinomas are very aggressive tumours. In most instances, the tumour is so large and the infiltration is so extensive that complete surgical resection cannot be achieved. Radiotherapy and chemotherapy are additional options, either single or combined. High-dose chemotherapy and autologous bone marrow transplantation have been considered as a form of treatment [241]. Prognosis of SNUC is dismal, with a median survival of 4 months to 1 year [86, 114]. In our experience survival after 2 years is less than 40%.

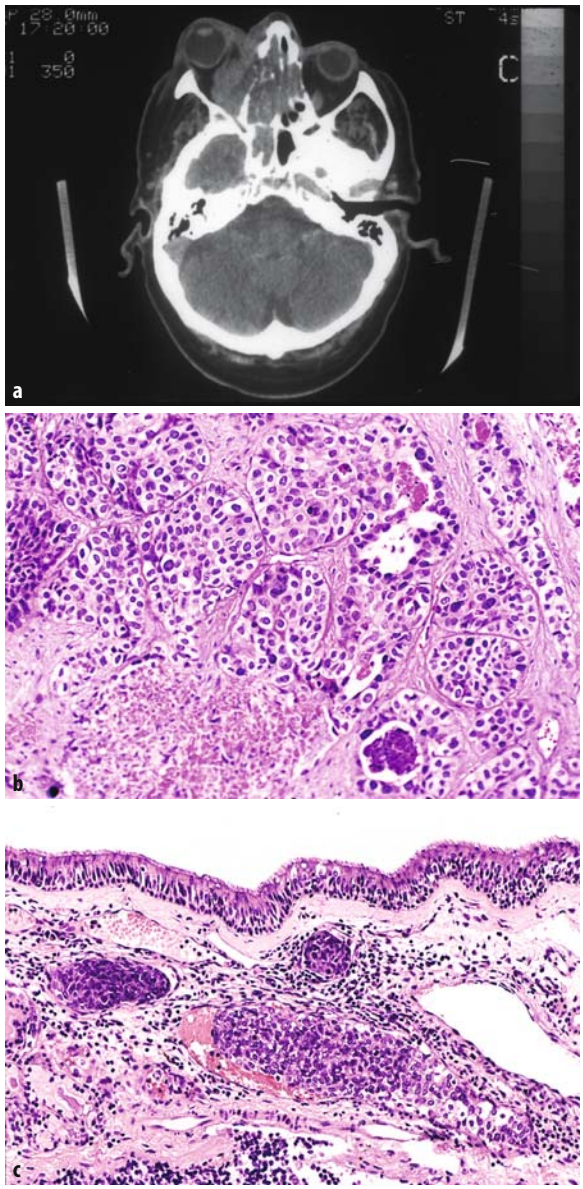

Fig. 2.10. Sinonasal undifferentiated carcinoma (SNUC) **a** Extensive neoplastic growth invading ethmoid, orbit and sphenoid at the left and also the right ethmoid. Courtesy of Prof. J. Traserra, Barcelona, Spain. **b** Nests of small to intermediate epithelial cells showing markedly atypical nuclei and areas of necrosis. **c** Frequent foci of intra-vascular invasion

2.11.4 Small Cell (Neuroendocrine) Carcinoma

ICD-O:8041/3

This is a high-grade malignant epithelial tumour with histological features similar to small cell carcinoma of the lung [226]. Variable degrees of neuroendocrine differentiation may be demonstrable by electron microscopy or immunohistochemistry, but have not always been required for diagnosis [176]. Before placing a tumour within this category, a differential diagnosis of a primary tumour from the lung must be ruled out.

This type of tumour has been well documented in various head and neck territories, mainly in the parotid gland and in the larynx. In the sinonasal tract, where they are distinctly uncommon, small cell neuroendocrine carcinomas have been less precisely characterised, and so far no unanimous consensus has been reached with regard to the way they have to be separated from other small cell tumours, either round or undifferentiated, occurring in this region [51, 132, 151, 191, 208, 210, 229, 264]. Table 2.2 provides the current criteria most widely accepted for their recognition.

Small cell neuroendocrine carcinoma of the sinonasal region is considered to derive from cells with neuroendocrine differentiation occasionally found in the seromucous glands. In some cases the tumour grows surrounding the seromucous glands of the lamina propria, as if it were originating from them. They give rise to nests, cords and sheets of small, undifferentiated cells, with moulded nuclei and scanty cytoplasm. Immunohistochemistry exhibits a positive reaction for low molecular weight cytokeratins and EMA, as well as variable positivity for neuron-specific enolase, Leu-7, CD56, synaptophysin and chromogranin. At least two neuroendocrine markers should demonstrate positivity [199]. Diligent searching and expert hands usually demonstrate neurosecretory granules by electron microscopy.

Although its prognosis seems to be somewhat better than that of SNUC, or for similar tumours of the lung, small cell neuroendocrine carcinoma is a high-grade malignancy. Treatment should be a combination of surgery and radiotherapy, plus chemotherapy.

2.11.5 Primary Sinonasal Nasopharyngeal-Type Undifferentiated Carcinoma

ICD-O:8082/3

Although nasopharyngeal carcinoma (NPC), also known as lymphoepithelioma, almost invariably arises in the nasopharynx, "bona fide" primary sinonasal nasopharyngeal-type undifferentiated carcinomas (PSNPC) have recently been reported [127]. Due to the undifferentiated appearance of cells in NPC and PSNPC, these tumours may be lumped together with SNUC if unaware of their differences [48, 80, 127]. SNUC does not arise in the nasopharynx, but bulky lesions may extend into this region. Also, NPC may extend from the nasopharynx into the sinonasal region. The distinction between these tumours can generally be made on purely histological grounds, since SNUC lacks the lymphoplasmacytic cell infiltrate seen in most cases of NPC and PSNPC. Immunohistochemistry and in

Table 2.2. Sinonasal undifferentiated tumors. Immunohistochemistry and genetics.

	CK	NSE	S-100	CG	SYN	NF	EBV	L	MIC-2	t11;22	Ampl N-myc
SNUC	+	±	–	–	–	–	–	–	–	–	–
SCC	+	+	–	±	+	–	–	–	–	–	–
PSNPC	+	–	–	–	–	–	+	–	–	–	–
SNML	–	–	–	–	–	–	+	+	–	–	–
PNET	–	+	+	±	+	–	–	–	+	+	–
ONB	–	+	(+)	+	+	+	–	–	–	–	–
MNB	–	+	–	+	+	+	–	–	–	–	+

SNUC sinonasal undifferentiated carcinoma, *SCC* small cell (neuroendocrine) carcinoma, *PSNPC* primary sinonasal nasopharyngeal-type carcinoma, *SNML* sinonasal malignant lymphoma, *PNET* primitive neuroectodermal tumour, *ONB* olfactory neuroblastoma, *MNB* metastatic neuroblastoma, *CK* cytokeratin, *NSE* neuronal specific enolase, *S-100* Protein S-100, *CG* chromogranin, *SYN* synaptophysin, *NF* neurofilaments, *EBV* Epstein-Barr virus, *L* lymphoma markers, *MIC-2* CD99, *t(11;22)* EWS-FLI1, *Ampl* amplification, *(+)* positive only in sustentacular cells

situ hybridisation are of great help in difficult cases. All three, NPC, PSNPC, and SNUC, react positively for low molecular weight cytokeratins and EMA. In contrast, NPC and PSNPC are positive for EBV, whereas SNUC is negative. Until very recently, confusion of NPC and PSNPC with SNUC has led to the belief that some SNUC were related to EBV. The sharp distinction of these entities is crucial because NPC and PSNPC have a better prognosis and are more responsive to radiation therapy than SNUC.

2.11.6 Malignant Melanoma

ICD-O:8720/3

Sinonasal melanomas represent between 0.5 and 1.5% of all melanomas [25, 82, 157] and between 3 and 20% of sinonasal malignant neoplasms [25, 74]. They most frequently develop after the fifth decade of life [25, 42, 250] and seem to originate from melanocytes present in the mucosa of the respiratory tract [25, 58, 275]. In our experience, it is not uncommon to see melanomas arising in an area of squamous metaplasia . In contrast to Caucasians, black Africans often show visible pigmentation at sites corresponding with the common locations of intranasal melanomas, of which they have a higher incidence [148]. Although there is not a significant sex predilection, men seem to be affected more than women [25, 29, 42]. The signs and symptoms of presentation of sinonasal melanomas are not specific. Epistaxis and nasal obstruction are frequent when located in the nasal cavity.

Grossly sinonasal malignant melanomas are either pigmented (black-brown) or non-pigmented (pink-tan) lesions. In the nasal cavity, they commonly arise in the anterior portion (Fig. 2.11a) of the septum and present as tan-brown polypoid formations, with occasional ulcerated and hemorrhagic areas. When arising within sinuses, they present as extensive and widely infiltrative tumours. The development of an intranasal malignant melanoma in an inverted papilloma has been reported [99].

The histological features of sinonasal melanomas may be as polymorphic as in their cutaneous counterpart. Metastatic disease needs to be ruled out, before they are labelled as primary tumours. Primary melanomas may be recognised by the presence of junctional activity (Fig. 2.11c) or by the finding of an intraepithelial component in the adjacent mucosa; nevertheless, these features are usually lost in advanced stages of the disease. Histologically, melanomas are composed of medium to large cells that may be polyhedral, round, fusiform (Fig. 2.11b), pleomorphic, microcytic, or a mixture of them. Usually, they have finely granular cytoplasm and nuclei with one or more eosinophilic nucleoli. Mitotic activity is prominent. A rare balloon cell variant with clear cytoplasm may mimic various types of clear cell tumours (see Chap. 5). Osteocartilaginous differentiation has also been observed [244]. The cells of sinonasal melanoma grow in solid, loosely cohesive, storiform, pseudo-alveolar or organoid patterns [25]. Two-thirds of sinonasal melanomas contain some intracytoplasmic brown pigment (Fig. 2.11d) [25], which has to be confirmed as melanin by Masson-Fontana or Grimelius silver stains. However, in the sinonasal tract non-pigmented melanomas are not uncommon; in our Barcelona series up to 40% of the sinonasal melanomas are amelanotic. When melanin is scarce or is not found, diagnosis may be difficult, and special techniques are mandatory. Immunohistochemically, the cells of amelanotic melanomas are negative for cytokeratin and positive for vimentin, S-100 protein and HMB-45 [65, 82, 209], as well as anti-tyrosinase and other newly reported markers [207]. Electron microscopy reveals the presence of pre-melanosomes and/or melanosomes.

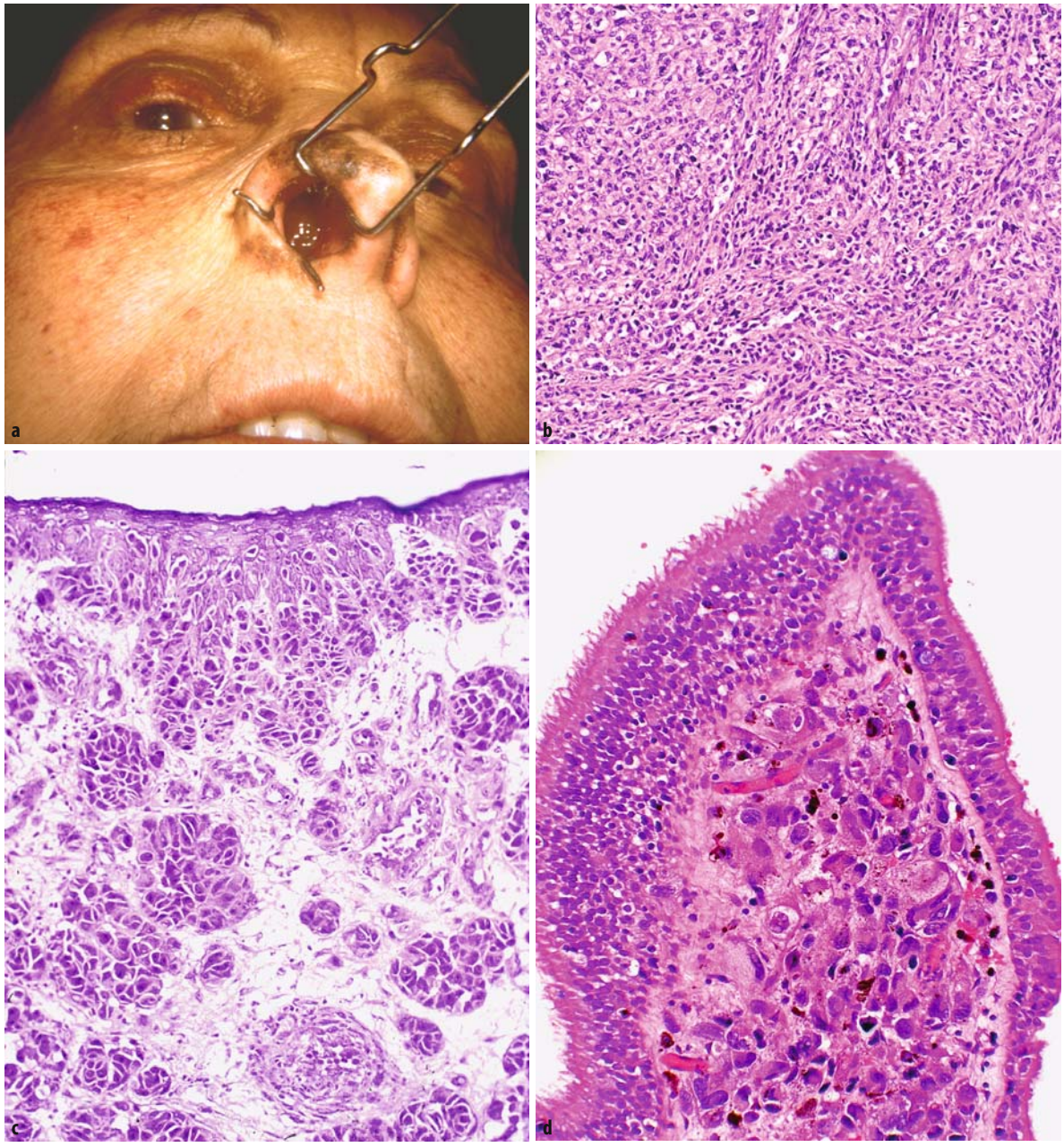

Fig. 2.11. Sinonasal malignant melanoma. **a** Darkly pigmented polypoid lesion of the anterior nasal cavity in contiguity with a pigmented lesion of nasal skin. Courtesy of Prof. J. Traserra, Barcelona, Spain. **b** Spindle cell non-pigmented malignant melanocytes with storiform pattern. **c** Nests of non-pigmented, invasive malignant melanocytes arising from metaplastic squamous epithelium showing junctional activity. **d** Pigmented malignant melanocytes underneath ciliated respiratory epithelium

The differential diagnosis of amelanotic malignant melanoma of the sinonasal tract comprises a long list of entities. Epithelioid melanomas mainly have to be distinguished from non-keratinising squamous cell carcinomas, but also from other large cell carcinomas as well as from epithelioid malignant schwannomas [76] and from metastases. Microcytic melanoma may mimic SNUC and other small round cell tumours (Table 2.2). Spindle-cell melanoma may be mistaken for a variety of spindle-cell sarcomas (see Sects. 2.11.13 to 2.11.17).

The prognosis and management is related to the peculiar biology of the tumour. The prognostic significance of the level of local invasion, as established for cutaneous melanomas, does not apply to mucosal melanomas because of the absence of histological landmarks analogous to the papillary and reticular dermis; nevertheless, inva-

sion deeper than 0.5 mm is associated with decreased survival [25].

Although many of the patients do not show initial lymph node involvement or disseminated metastases [25, 83, 107] and have stage I disease at the time of initial diagnosis, the prognosis is bad due to a high recurrence rate [250]. This recurrence appears to be related to the multicentricity of the tumours and to the anatomic characteristics of the region that preclude adequate resection, which is the treatment of choice [29, 256]. The utility of radiotherapy is controversial, but it can be of use in unresectable cases or to control recurrences [29, 95]. Immunotherapy and chemotherapy are also used for metastatic disease [256]. Five-year survival of sinonasal melanoma is reportedly under 35% [29, 250, 256]. The mean survival has not improved during the past 15 years [32]. In our Barcelona series, the 5-year survival rate of 35% is similar to that of sinonasal squamous cell carcinoma. Patients with primary nasal melanomas had a significantly better 5-year survival rate than patients with melanomas from other head and neck sites [154].

2.11.7 Olfactory Neuroblastoma

ICD-O:9522/3

Olfactory neuroblastoma (ONB) is defined as a malignant tumour composed of neuroblasts derived from the olfactory membrane [14, 175, 246, 257]. Synonyms include early terminology such as esthesioneuroepithelioma, esthesioneurocytoma and esthesioneuroblastoma. The site of origin of ONB is confined to the olfactory mucosa that lines the upper part of the nasal cavity [181]. On rare occasions ONB predominantly involves the superior aspect of the cribiform plate and grow as intracranial masses [15, 186]. Before establishing a diagnosis of the extremely rare entity known as "ectopic" olfactory neuroblastoma, which implies absence of involvement of the olfactory membrane, other sinonasal small round cell tumours have to be carefully ruled out (Table 2.2).

Olfactory neuroblastoma has a bimodal age distribution with peaks in the 2nd and 6th decades [70]. This clearly differs from adrenal neuroblastoma, with most cases arising in children under 4 years of age. Both sexes are equally affected. Nasal obstruction, rhinorrhoea and epistaxis are the most common presenting symptoms.

Grossly, the tumours are often unilateral, presenting as smooth polypoid or fungating masses of fleshy consistency and yellow to pink colour (Fig. 2.12a).

At low magnification, ONB exhibits one of two main patterns of growth [176]. Most often, it presents a lobular arrangement with well-defined groups of tumour cells separated by abundant oedematous stroma. Less frequently, the tumour grows as diffuse sheets of cells with scanty, but highly vascular stroma. The neoplastic neuroblasts are typically small, showing round to oval nuclei with stippled chromatin, absent or small nucleoli, and minimal cytoplasm. They are commonly separated by a neurofibrillary matrix formed by neuronal cell processes in which axons may be demonstrable by conventional silver stains. This background, seen in about 85% of ONBs, is the most helpful diagnostic feature (Fig. 2.12b). The Homer-Wright type of rosettes is quite characteristic of ONB; however, they are less commonly seen. They form when the tumour cells surround the neurofibrillary matrix in collar-like arrangements. Even more rare are the true olfactory Flexner-Wintersteiner type of rosettes, which depict well-defined lumina lined by columnar cells resembling olfactory epithelium. These cells generally have basally located nuclei and merge with the adjacent neuroblasts without any intervening basal lamina. Perivascular pseudorosettes, formed by tumour cells arranged around capillaries, are of no diagnostic value, for they may be found in several types of neoplasms.

The scheme proposed by Hyams [122] to grade ONB into four groups carries diagnostic and prognostic implications (Table 2.3). The differential diagnosis of ONB includes a wide variety of small round cell tumours arising in the sinonasal region (Table 2.2). Immunohistochemically, ONB shows diffuse positivity for NSE and synaptophysin, but is less often positive for chromogranin. In tumours with a nesting pattern, sustentacular cells are positive for S-100 protein, but generally negative for cytokeratin, although in ONB with a nesting pattern a few tumours may exhibit focal staining for low molecular weight cytokeratins. They are negative for EMA. Neurofilament protein and other markers of neural differentiation are more often expressed in tumours with diffuse, sheet-like patterns [53, 87, 246, 268]. Electron microscopy shows evidence of neuroblastic differentiation, demonstrating neuritic processes, neurotubules and membrane-bound dense-core granules [131, 159, 247]. The human analogue of achaete-scute gene (HASH1), expressed in immature olfactory neurons, is also expressed in ONB [45]. Conversely, the olfactory marker protein [182], expressed exclusively in mature olfactory neurons, is not. ONB lacks CD 99 (MIC-2) expression, as well as the t(11;22) translocation characteristic of primary neuroectodermal tumour (PNET) [13, 263]. It also lacks the molecular genetic changes of sympathetic neuroblastoma, which, in children, may be metastatic to the sinonasal region.

Staging of ONB is based on the Kadish system [129], in which stage A disease is confined to the nasal cavity, stage B to the nasal cavity and paranasal sinuses, and stage C shows local or distant spread beyond the nasal cavity or sinuses. This correlates with prognosis [70]. Necrosis is the single histological feature that seems to correlate with poor survival [175]. About two-thirds of recurrences are in the form of local disease, whereas locoregional recurrences, with intracranial extension or involvement of cervical lymph nodes, represent about 20%, and distant

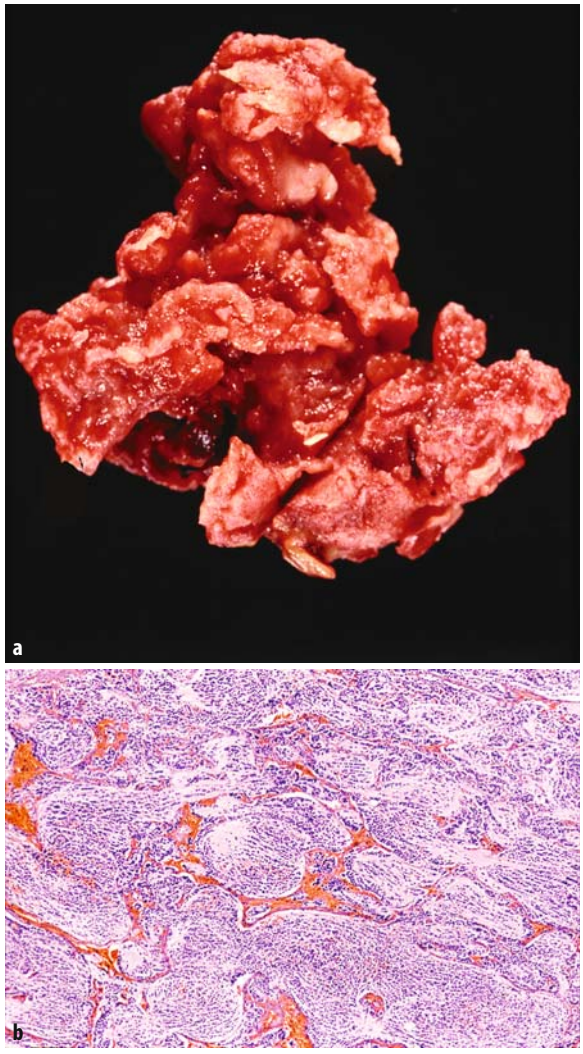

Fig. 2.12. a Olfactory neuroblastoma: polypoid mass of fleshy consistency and pink colour. **b** Well-differentiated olfactory neuroblastoma: nests of small round neuroblasts embedded in a neurofibrillary matrix are surrounded by delicate networks of capillary blood vessels

metastases account for the rest [70]. Distant metastases mainly involve bone and lung [68]. Complete surgical excision, often followed by radiation therapy and/or chemotherapy, seems to be the treatment of choice [14, 179]. In advanced ONB, high-dose chemotherapy and autologous bone marrow transplantation has been used [68, 188].

2.11.8 Primitive Neuroectodermal Tumour

ICD-O:9364/3

Approximately 9% of extraosseous Ewing's sarcoma/primitive neuroectodermal tumour (PNET) arise in the head and neck region [176]. This tumour is composed of uniform, small, undifferentiated, primitive neuroectodermal cells (Fig. 2.13a) [149]. The great majority of these tumours will react strongly with antibodies against the MIC-2 (CD99) protein product (Fig. 2.13b). This marker is of considerable value, but it is by no means specific. A growing number of other neoplasms expressing this protein have been documented. Among these are T-cell lymphomas [263]. The standard translocation t(11; 22) (q24; q12) of PNET [260] results in the fusion of the EWS-FLI1 genes. The detection of the chimeric transcript by techniques of molecular biology confirms the diagnosis [238]. We have seen one example of PNET arising from the maxillary antrum [39], which ultrastructurally showed rudimentary neuritic differentiation, as well as scanty microtubule formation. This raised the differential diagnostic dilemma of "ectopic olfactory neuroblastoma"; nevertheless, the tumour cells were positive for MIC-2 and showed the t(11;22)(q24;q12) translocation, findings that are characteristically negative in ONB [13].

2.11.9 High-Grade Sinonasal Adenocarcinomas

2.11.9.1 Intestinal-Type Adenocarcinoma

ICD-O:8144/3

This is a tumour with histological features resembling colorectal adenocarcinoma [126, 220]. It is considered to originate through intestinal metaplasia of the ciliated respiratory cells lining the schneiderian membrane. This tumour is the most common type of sinonasal adenocarcinoma, representing about 6–13% of malignancies developing in the sinonasal tract [41, 105, 216]. Metastasis from gastrointestinal adenocarcinoma should be ruled out before a tumour is labelled as a primary of this region. These tumours are strongly associated with exposure to different types of dust, mainly hardwood, but also softwood dusts, as well as leather dust [4, 5, 47, 102, 123, 124, 142]. About 20% of sinonasal intestinal-type adenocarcinomas seem to be sporadic, without evidence of exposure to industrial dusts [4].

Grossly, they have a fungating appearance with either polypoid or papillary features. Occasionally, they may have a gelatinous consistency resembling a mucocele. The most common location is the ethmoidal region [17]. Histologically, the tumour is mainly composed of columnar mucin-secreting cells and goblet cells [17]. Some well-differentiated tumours may also contain resorptive cells, argentaffin cells and Paneth cells. Endocrine-amphicrine enteric differentiation may occasionally be found [222]. Metaplastic and atypical changes have been observed in adjacent pre-neoplastic epithelium [270]. These tumours

Table 2.3. Olfactory neuroblastoma. Hyams Grading Scheme [122].

Histologic grades	1	2	3	4
Lobular architecture	Present	Present	±	±
Mitotic activity	Absent	Present	Prominent	Marked
Nuclear pleomorphism	Absent	Moderate	Prominent	Marked
Fibrillary matrix	Prominent	Moderate	Slight	Absent
Rosettes	H-W ±	H-W ±	Flexner ±	Absent
Necrosis	Absent	Absent	Occasional	Common
Calcification	±	±	Absent	Absent

H-W Homer-Wright rosettes, ± present or absent

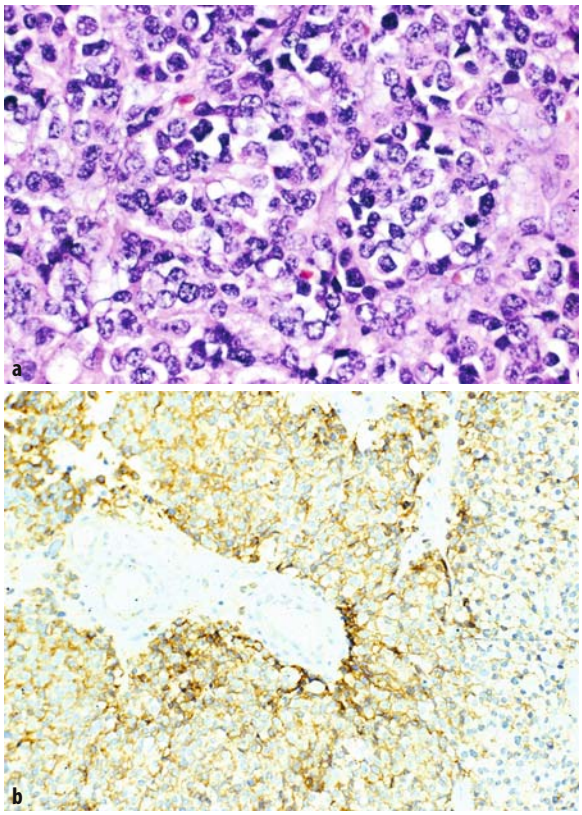

Fig. 2.13. Primitive neuroectodermal tumour (PNET). **a** Monotonous proliferation of small, round, undifferentiated cells. **b** CD99-positive immune reaction at the cellular membrane

depict different histological patterns that may be predominantly papillary, glandular, compact, mucinous or mixed [17, 23]. Papillary tumours mainly consist of elongated outgrowths lined by intestinal-type cells with markedly atypical pseudostratified nuclei (Fig. 2.14a). Although most of them are high-grade tumours, low-grade forms (Fig. 2.14b) mimicking colonic villous adenoma may occasionally occur [174]. The glandular pattern resembles common-type intestinal adenocarcinoma. Compact or solid forms show poorly differentiated nests of cells in which glandular formation is rarely seen. In the mucinous pattern, more than 50% of the tumour is composed of dilated mucin-filled glands lined by columnar mucin-secreting epithelium, and lakes of mucin containing fragmented epithelial elements (Fig. 2.14c). Other mucinous tumours show mucin-filled cells with the pattern of "signet-ring" cell carcinoma. Various attempts have been made to correlate histopathological grading and typing with clinical behaviour [78, 81, 140].

Features such as cytologic atypia, high mitotic rate and areas of necrosis, which are common findings in most intestinal-type adenocarcinomas, help to distinguish the high-grade variants from rare low-grade intestinal-type adenocarcinomas and from mucoceles. The lack of epidermoid and squamous differentiation separates these tumours from mucoepidermoid and adenosquamous carcinomas. Immunohistochemistry and electron microscopy have confirmed the enteric differentiation of the tumour cells [24]. These tumours are positive for a wide spectrum of cytokeratin markers, whereas they are only occasionally positive for carcinoembryonic antigen [166]. Intestinal-type adenocarcinomas are frequently but not always positive for cytokeratin 7, while most express cytokeratin 20 and CDX-2, two markers related to intestinal differentiation [79]. The prognosis for high-grade intestinal-type adenocarcinoma is poor. Recurrences and subsequent deeply invasive local growth are frequent; however, lymph node and distant metastases are rare [17, 78, 142]. Treatment of choice is complete surgical resection followed by radiotherapy.

2.11.9.2 Salivary-Type High-Grade Adenocarcinomas

Adenoid Cystic Carcinoma
ICD-O:8200/3

Adenoid cystic carcinoma (see Chap. 5) is the most common malignant salivary-type of tumour of the upper

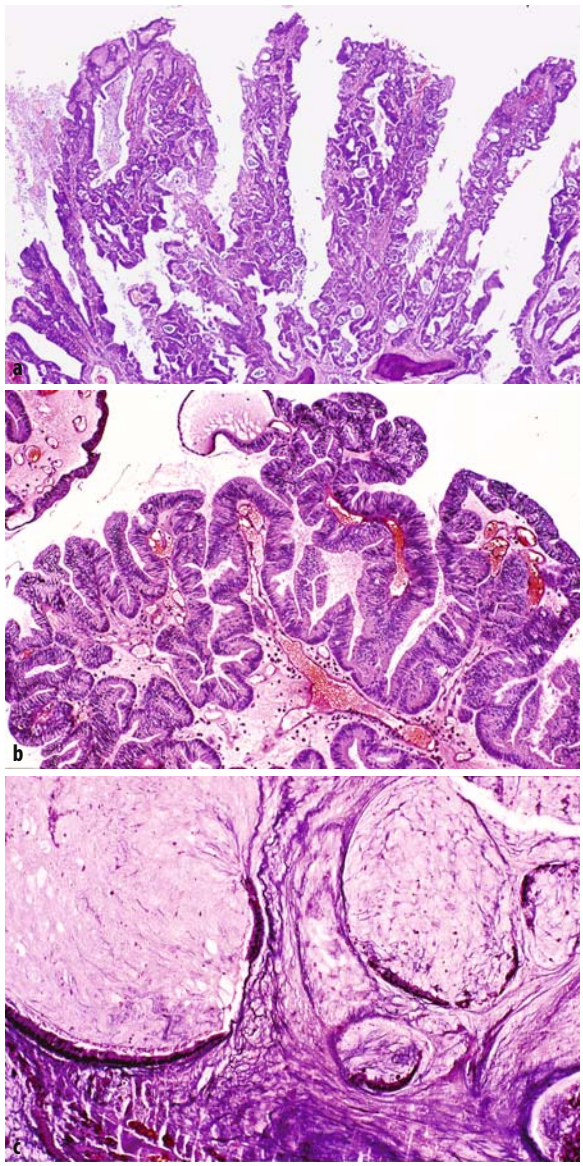

Fig. 2.14. Intestinal-type adenocarcinoma. **a** Papillary outgrowth of intestinal-like malignant epithelium. Destruction of sinonasal bone at the bottom. **b** Low-grade variant mimicking villous adenoma of the colon. **c** Mucinous variant mimicking mucocele

respiratory tract and constitutes 5–10% of all sinonasal malignancies [43, 105, 206]. It is most common in the maxillary antrum, followed by the nasal cavity [60], although ethmoid, sphenoid and frontal sinuses may also be involved [110, 169, 255].

Other Salivary-Type High-Grade Adenocarcinomas

With the exception of adenoid cystic carcinoma, these tumours are quite rare in the sinonasal region. Although most salivary duct carcinomas (SDCs) arise from the major salivary glands, the development of this highly aggressive tumour from the seromucous glands of the upper respiratory tract may occasionally occur. We have seen one example of SDC originating in the maxillary antrum, in which the characteristic ductal pattern, with comedo-type necrosis, was only evident in the metastases to the submandibular lymph nodes. The primary tumour was initially classified as adenocarcinoma not otherwise specified (NOS) due to the absence of convincing diagnostic features [40]. Carcinoma ex pleomorphic adenoma may also occur in the sinonasal tract [110].

2.11.10 Low-Grade Sinonasal Adenocarcinomas

Low-grade adenocarcinomas arising primarily within the sinonasal tract are an uncommon and heterogeneous group of tumours [23, 113, 139, 150]. Some of these neoplasms show apparent histological continuity with the normal surface epithelium of the sinonasal mucosa, whereas others are of salivary gland origin. All have better prognosis and different clinical presentation than their high-grade counterpart. With the exception of the well-differentiated, low-grade, adenocarcinomas of intestinal type, no correlation with occupational activities has been found in these tumours.

2.11.10.1 Non-Salivary-Type Low-Grade Adenocarcinomas

Non-salivary-type low-grade sinonasal adenocarcinomas are a distinctive group of tumours comprising well-differentiated tubular or papillary structures, or a combination of both. They are lined by a single layer of cuboidal or columnar cells that display uniform round or oval nuclei, inconspicuous nucleoli, minimal cytologic atypia and scarce mitotic figures. They are locally infiltrative and have a tendency towards local recurrence [113].

Different histological patterns may be recognised: papillary, glandular, mucinous, trabecular, cribriform and clear cell. The papillary pattern is characterised by complex papillary fronds lined by bland columnar cells that may occasionally mimic oncocytic (columnar) cell papilloma. Quite similar tumours also develop in the nasopharynx [267]. The glandular pattern may simulate adenoma; nevertheless, the presence of closely packed glands, forming back-to-back arrangements, indicates the true malignant nature. Mucinous tumours have to be distinguished from mucoceles and from mucinous adenocarcinoma of intestinal or salivary type [20, 224]. The trabecular pattern may resemble acinic cell carcinoma [200]. The cribriform arrangements have to be distinguished from low-grade salivary duct carcinoma of salivary glands [62]. The clear cell type has to be separated from the salivary-type tumours with clear cells and

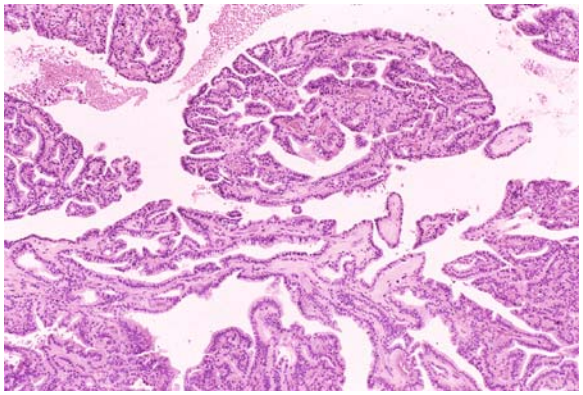

Fig. 2.15. Tubulopapillary carcinoma: low-grade proliferation of cuboidal to columnar epithelial cells forming tubules at the centre and papillae at the surface

from metastatic renal cell carcinoma [31, 280]. A tubulopapillary variant has recently been reported (Fig. 2.15) [234] that has to be differentiated from terminal tubulus adenocarcinoma of the nasal seromucous glands [139].

2.11.10.2 Salivary-Type Low-Grade Adenocarcinomas

Mucoepidermoid carcinoma, polymorphous low-grade adenocarcinoma (Fig. 2.16) and acinic cell carcinoma originate only on rare occasions from the seromucous glands of the sinonasal mucosa [43, 110, 150, 190, 200, 239]. Most mucoepidermoid carcinomas of the sinonasal tract are low-grade. Some large oncocytic tumours of the sinonasal tract may behave in a locally aggressive fashion and are better classified as low-grade adenocarcinomas [55, 103, 110]. All these tumours are dealt with in detail in Chap. 5 on salivary glands. Their main differential diagnoses are other salivary- or non-salivary-type low-grade adenocarcinomas.

2.11.11 Sinonasal Malignant Lymphomas

Malignant lymphomas of the sinonasal region comprise approximately 6% of all sinonasal malignancies [134]. In our Barcelona series, they account for 9.5% (Table 2.1). In western countries, about 50% of sinonasal lymphomas are of B-cell type, whereas the other 50% mostly showed NK/T-cell lineage [38]; nevertheless, other reports point to more variable rates [3, 72, 77, 85]. Conversely, in oriental populations most primary lymphomas of the nasal cavity and nasopharynx are of NK/T cell lineage [49, 50, 52, 92, 233].

Sinonasal B-cell lymphomas are in general composed of a diffuse proliferation of large lymphoid cells, or of a

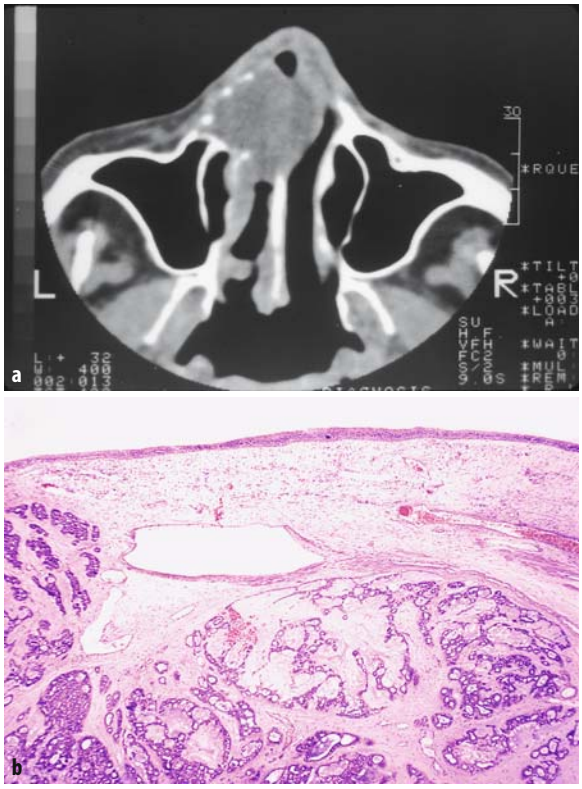

Fig. 2.16. Polymorphous low-grade adenocarcinoma. **a** CT scan showing an irregularly nodular lesion destroying the anterior nasal septum. Courtesy of Prof. J. Traserra, Barcelona, Spain. **b** Variegated glandular arrangements composed of tubules with bland cellularity are seen beneath respiratory epithelium

diffuse mixed pattern of small and large cells. They infiltrate and expand the subepithelial soft tissue and may extend into the underlying bone. Sinonasal B-cell lymphomas lack epitheliotropism, polymorphous cell infiltrate, angiocentricity, prominent necrosis, and fibrosis. They are usually positive for B-cell markers (CD20 and CD79a) and negative for NK/T cell markers. κ light chain restriction is seen more often than λ restriction. They are often negative for EBV markers. Radiotherapy and chemotherapy is the standard treatment for advanced tumours [213].

Sinonasal NK/T cell lymphomas were labelled in past decades with terms such as "lethal midline granuloma", "polymorphic reticulosis" and "angiocentric T-cell lymphoma", among others. Until quite recently, non-B cell sinonasal lymphomas were considered as other forms of T-cell lymphoma, frequently displaying angiocentricity. Patients may present either with an obstructive mass or with mid-facial destructive lesions. Histologically, an angiocentric and angiodestructive infiltrate with extensive necrosis (Fig. 2.17a) is frequently seen. In NK/T-cell lymphoma, cells may be small, medium-sized, large, or anaplastic, and may show a conspicuous admixture of

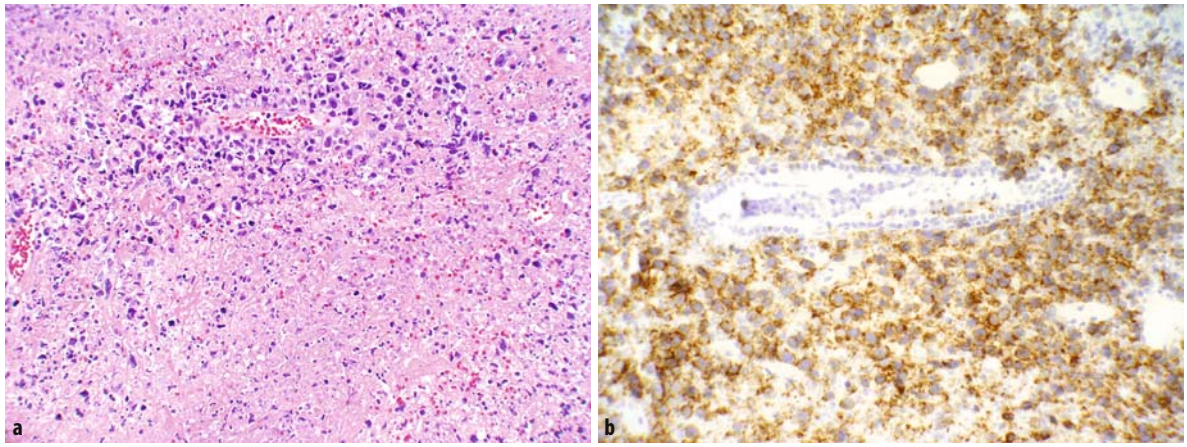

Fig. 2.17. Sinonasal NK/T lymphoma. **a** Angiocentric infiltrate of atypical lymphocytes with extensive necrotic areas. **b** Strongly positive CD56 immunoreaction

inflammatory cells. Pseudoepitheliomatous hyperplasia of the covering epithelium may occur [49]. NK/T cell lymphoma is almost always associated with EBV positivity. The most typical immunophenotypes are CD2+, CD56+ (Fig. 2.17b), surface CD3–, and cytoplasmic CD3epsilon+. Most cases are also positive for cytotoxic granule-associated proteins (granzyme B, TIA-1 and perforin). They are usually negative for other T and NK-cell associated markers. Sinonasal lymphomas demonstrating CD3epsilon+, CD56–, cytotoxic molecule+, and EBV+ are also included within the NK/T category. The commonest cytogenetic abnormality found in NK/T-cell lymphoma is the 6q-22-23 deletion [233]. The prognosis of nasal NK/T-cell lymphoma is variable. Some patients respond well to therapy and others die of disease despite aggressive therapy [52].

Sinonasal malignant lymphomas of either B-cell or T-cell derivation need a careful differential diagnosis with other small round cell tumours (Table 2.2) and with extramedullary plasmacytoma [6, 46], as well as with extramedullary tumours composed of myeloid or lymphoid blasts [133].

2.11.12 Extramedullary Plasmacytoma

ICD-O:9731/3

Plasmacytoma of the sinonasal tract appears as a diffuse infiltration of mature plasma cells of the mucosa; occasionally, tumour cells are less differentiated, and diagnosis may be difficult on a histologic basis [2, 6, 46, 185]. Immunohistochemical staining for CD138 and κ and λ chains may be helpful. Full examination of the patient is required to exclude disseminated disease.

2.11.13 Fibrosarcoma

ICD-O:8810/3

Fibrosarcoma of the sinonasal tract occurs across a wide age range, most commonly causing obstruction or epistaxis. The histologic appearance is that of a spindle cell lesion, with fascicles or bundles of neoplastic cells intersecting at various angles, sometimes with a herringbone pattern. Most sinonasal fibrosarcomas have a low-grade appearance, with moderate cellularity and a low mitotic rate [111]. In accordance, the behaviour is more often characterised by repeated local recurrences, while distant metastases are rare. The differential diagnosis includes desmoid fibromatosis, leiomyosarcoma, nerve sheath tumours, spindle cell carcinoma and melanoma.

2.11.14 Malignant Fibrous Histiocytoma

ICD-O:8830/3

Malignant fibrous histiocytoma is a high-grade sarcoma of adulthood histologically consisting of a proliferation of spindle cells arranged in a storiform pattern, intermixed with atypical pleomorphic, often multinucleated giant cells. In the sinonasal tract it presents as a highly aggressive and destructive lesion, with bone invasion and extension in adjacent structures [201]. Before a diagnosis of malignant fibrous histiocytoma is rendered, other pleomorphic malignant tumours, like leiomyosarcoma, osteosarcoma and sarcomatoid carcinoma should be excluded by means of immunohistochemical or ultrastructural analysis.

2.11.15 Leiomyosarcoma

ICD-O:8890/3

Leiomyosarcoma of the sinonasal tract is an extremely rare neoplasm, with identical histological appearance and immunoprofile to the soft tissue counterpart [91]. If the tumour is limited to the nasal cavity the prognosis is good, and according to Kuruvilla et al. [144], sinonasal leiomyosarcoma can be regarded as a locally aggressive neoplasm with limited metastatic potential that should be treated by surgery alone. Distinction from sinonasal leiomyoma is based on mitotic activity and cellular atypia.

2.11.16 Rhabdomyosarcoma

ICD-O:8900/3

Rhabdomyosarcoma is the most common sinonasal malignancy of the paediatric age, but it is also observed in adults [37, 116]. The most common histologic subtypes are the embryonal and the alveolar [37]. The overall 5-year survival is around 40%; adult age and alveolar subtype are adverse prognostic factors. Treatment includes a combination of radiotherapy and chemotherapy, with surgical resection reserved for residual disease. The risk of neck involvement is high.

2.11.17 Malignant Peripheral Nerve Sheath Tumour

ICD-O:9560/3

Malignant peripheral nerve sheath tumour (MPNST) of the sinonasal tract is a very rare neoplasm [163] that is probably under-recognised due to the lack of reproducible histologic criteria and to the tendency of these tumours to be negative for the commonly used immunohistochemical markers of nerve sheath differentiation. Only in some cases can the diagnosis be based on the identification of a pre-existing neurofibroma. Histologically, MPNST is a moderately to highly cellular spindle cell proliferation, with variable mitotic activity and areas of necrosis. A variant composed of epithelioid cells has been described in the sinonasal cavities (Fig. 2.18) [76]. Some tumours may show morphologic and immunohistochemical features of skeletal muscle differentiation and are designated "malignant triton tumours" [138].

2.11.18 Teratocarcinosarcoma

ICD-O:8980/3

The term "teratocarcinosarcoma" is designated to an unusual entity in which a malignant sinonasal teratomatous tumour also shows features of carcinosarcoma

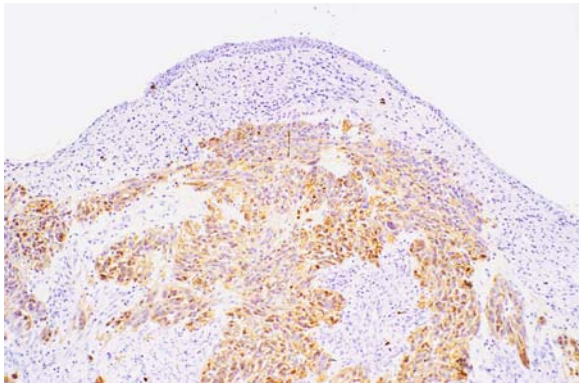

Fig. 2.18. Sinonasal malignant epithelioid schwannoma: marked S-100 protein positivity in a large cell malignant neoplasm, mimicking amelanotic melanoma

[112]. Patients suffering from this malignancy are exclusively adults (age range 18–79 years; mean 60 years) [64, 75, 112, 156, 195, 227]. There is a male predominance and symptoms are non-specific with nasal obstruction and epistaxis produced by a nasal cavity mass (Fig. 2.19a) [112].

Histologically, sinonasal teratocarcinosarcoma (SNTCS) comprises a multiplicity of cell types of varying maturity (Fig. 2.19b). The epithelial component includes keratinising squamous epithelium, pseudostratified columnar ciliated epithelium and glandular structures lined by cuboidal and columnar cells including mucus cells. Masses of immature epithelial cells, some containing glycogen or mucin, are frequently found. "Foetal-appearing" clear cell squamous epithelium is a common finding and a very important diagnostic clue for some authors [112]. Neuroepithelial elements with rosettes and neuroblastoma-like areas are in most instances present. These epithelial and neuroepithelial elements occur in close relationship with each other and with mesenchymal elements, the most prominent of which are immature cells with oval or elongated nuclei. The mesenchymal cells may exhibit skeletal muscle differentiation with cross striations (Fig. 2.19c). Foci of cartilage, smooth muscle, adipose tissue and fibrovascular tissues may also be present. In spite of the common occurrence of areas having a variety of mature tissues, mitotic activity and cytological features of malignancy are demonstrable in the undifferentiated areas of both the epithelial and mesenchymal elements [75].

In order to achieve the correct diagnosis of SNTCS a thorough sampling of the specimen is required. Inadequate sampling may lead to mistaken diagnoses of esthesioneuroblastoma, squamous cell carcinoma, undifferentiated carcinoma, adenocarcinoma, malignant craniopharyngioma, malignant mixed tumour of salivary gland type, mucoepidermoid carcinoma, adeno-

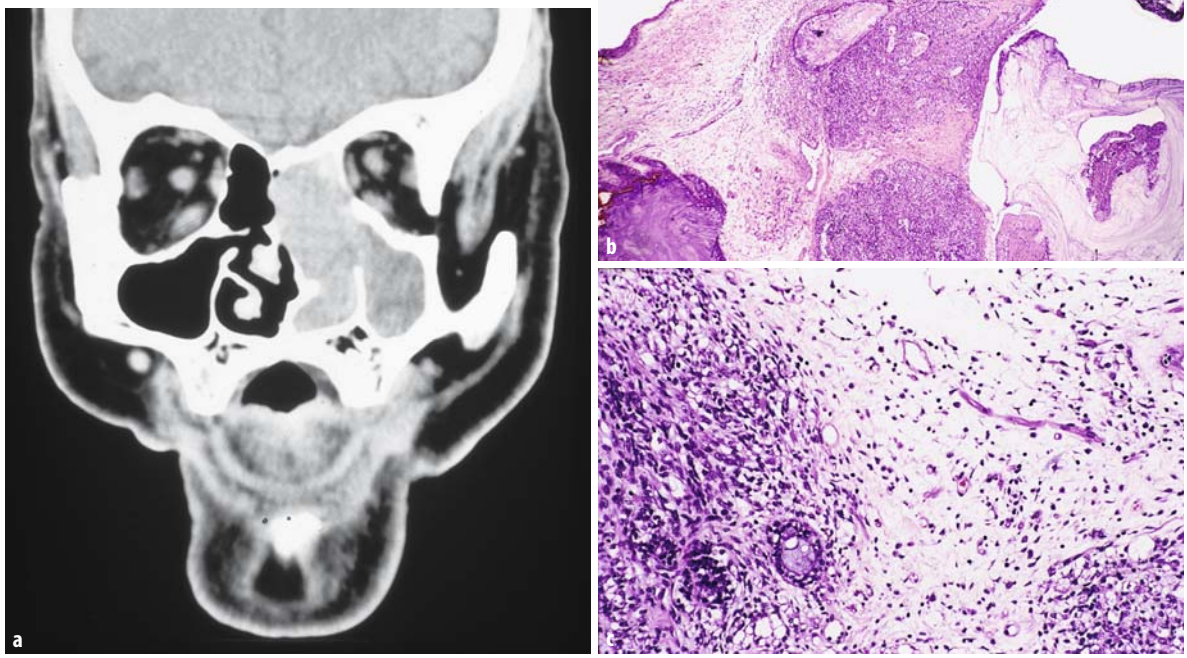

Fig. 2.19. Teratocarcinosarcoma. **a** CT scan showing massive destructive infiltration of the nasal cavity and maxillary sinus on the left. With permission [75] **b** Cystic spaces filled with mucin are partly covered by benign columnar epithelium and surrounded by immature blastematous tissue. **c** Immature glands surrounded by blastematous elements at the *lower left*; presence of immature striated muscle, *upper right* and *centre*

squamous carcinoma and others [105]. In contradistinction to malignant gonadal teratomas, which are frequently found in patients at a younger age, sinonasal teratocarcinosarcoma does not contain areas of embryonal carcinoma, choriocarcinoma or germinoma (seminoma), as seen in many germ cell tumours. This makes a germ cell origin of SNTCS unlikely [112]. The histogenesis of sinonasal teratocarcinosarcoma is debatable. The presence of neural tissue in these neoplasms raises the possibility that the origin could be in some way related to the olfactory membrane, or alternatively to the sinonasal membrane as a whole, since the olfactory membrane also develops from it [112].

Sinonasal teratocarcinosarcomas are locally aggressive tumours, with rapid invasion of soft tissues and bone, and metastasise to regional lymph nodes and sites, such as the lung. The average survival of a patient with 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 therapeutical approach with a combination of surgical resection, radiotherapy and chemotherapy is usually recommended [112].

References

1. Abdel-Latif SM, Baheeg SS, Aglan YI, Babin RW, Giltman LI (1987) Chronic atrophic rhinitis with fetor (ozena): a histopathologic treatise. Rhinology 25:117–120
2. Abemayor E, Canalis RF, Greenberg P, Wortham DG, Rowland JP, Sun NC (1988) Plasma cell tumors of the head and neck. J Otolaryngol 17:376–381
3. Abbondanzo SL, Wenig BM (1995) Non-Hodgkin's lymphoma of the sinonasal tract. A clinicopathologic and immunophenotypic study of 124 cases. Cancer 75:1281–1291
4. Acheson ED, Cowdell RH, Hadfield E, Macbeth RG (1968) Nasal cancer in woodworkers in the furniture industry. Br Med J 2:587–596
5. Acheson ED, Cowdell RH, Jolles B (1970) Nasal cancer in the Northamptonshire boot and shoe industry. Br Med J 1:385–393
6. Aguilera NS, Kapadia SB, Nalesnik MA, Swerdlow SH (1995) Extramedullary plasmacytoma of the head and neck: use of paraffin sections to assess clonality with in situ hybridization, growth fraction, and the presence of Epstein-Barr virus. Mod Pathol 8:503–508
7. Aktas D, Yetiser S, Gerek M, Kurnaz A, Can C, Kahramanyol M (1998) Antrochoanal polyps: analysis of 16 cases. Rhinology 36:81–85
8. Alobid I, Alos L, Blanch JL, Benitez P, Bernal-Sprekelsen M, Mullol J (2003) Solitary fibrous tumour of the nasal cavity and paranasal sinuses. Acta Otolaryngol 123:71–74
9. Alos L, Cardesa A, Bombí JA, Mallofré C, Cuchi A, Traserra J (1996) Myoepithelial tumours of salivary glands: a clinico-

pathologic, immunohistochemical, ultrastructural and flow-cytometric study. Semin Diagn Pathol 13:138–147
10. Alos L, Castillo M, Nadal A, Caballero M, Mallofre C, Palacin A, Cardesa A (2004) Adenosquamous carcinoma of the head and neck: criteria for diagnosis in a study of 12 cases. Histopathology 44:1–10
11. Anon JB (2003) Acute bacterial rhinosinusitis in pediatric medicine: current issues in diagnosis and management. Paediatr Drugs 5 [Suppl 1]:25–33
12. Apple D, Kreines K (1982) Case report. Cushing's syndrome due to ectopic ACTH production by a nasal paraganglioma. Am J Med Sci 283:32–35
13. Argani P, Perez-Ordonez B, Xiao H, Caruana SM, Huvos AG, Ladanyi M (1998) Olfactory neuroblastoma is not related to the Ewing family of tumours. Absence of EWS/FLI1 gene fusion and MIC2 expression. Am J Surg Pathol 22:391–398
14. Bailey BJ, Barton S (1975) Olfactory neuroblastoma management and prognosis. Arch Otolaryngol 101:1–5
15. Banerjee AK, Sharma BS, Vashista RK, Kak VK (1992) Intracranial olfactory neuroblastoma: evidence for olfactory epithelial origin. J Clin Pathol 45:299–302
16. Banks ER, Frierson HF, Mills SE et al. (1992) Basaloid squamous cell carcinoma of the head and neck. A clinicopathologic and immunohistochemical study of 40 cases. Am J Surg Pathol 16:939–946
17. Barnes L (1986) Intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Am J Surg Pathol 10:192–202
18. Barnes L, Bedetti C (1984) Oncocytic Schneiderian papilloma: a reappraisal of cylindrical cell papilloma of the sinonasal tract. Hum Pathol 15:344–351
19. Batra K, Chaudhary N, Motwani G, Rai AK (2002) An unusual case of primary nasal tuberculosis with epistaxis and epilepsy. Ear Nose Throat J 81:842–844
20. Batsakis JG (1970) Mucous gland tumors of the nose and paranasal sinuses. Ann Otol Rhinol Laryngol 79:557–562
21. Batsakis JG, el-Naggar AK (1992) Rhinoscleroma and rhinosporidiosis. Ann Otol Rhinol Laryngol 101:879–882
22. Batsakis JG, el-Naggar AK (1996) Cystic fibrosis and the sinonasal tract. Ann Otol Rhinol Laryngol 105:329–330
23. Batsakis JG, Holtz F, Sueper RH (1963) Adenocarcinoma of the nasal and paranasal cavities. Arch Otolaryngol 77:625–633
24. Batsakis JG, Mackay B, Ordóñez NG (1984) Enteric-type adenocarcinoma of the nasal cavity. An electron microscopic and immunocytochemical study. Cancer 54:855–860
25. Batsakis JG, Regezi JA, Solomon AR, Rice DH (1982) The pathology of head and neck tumors: Mucosal melanomas. Head Neck Surg 4:404–418
26. Beatty CW, Pearson BW, Kern EB (1982) Carcinoma of the nasal septum: experience with 85 cases. Otolaryngol Head Neck Surg 90:90–94
27. Begin LR, Rochon L, Frenkel S (1991) Spindle cell myoepithelioma of the nasal cavity. Am J Surg Pathol 15:184–190
28. Benninger MS, Ferguson BJ, Hadley JA, Hamilos DL, Jacobs M, Kennedy DW, Lanza DC, Marple BF, Osguthorpe JD, Stankiewicz JA, Anon J, Denneny J, Emanuel I, Levine H (2003) Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol Head Neck Surg 129:S1–S32
29. Berthelsen A, Andersen AP, Jensen S, Hansen HA (1984) Melanomas of the mucosa in the oral cavity and the upper respiratory passages. Cancer 54:907–912
30. Bosch A, Vallecillo L, Frias Z (1976) Cancer of the nasal cavity. Cancer 37:1458–1463
31. Brandwein M (2002) Renal cell-like carcinoma of the sinonasal tract. XXIV International Congress of the International Academy of Pathology. Amsterdam. The Netherlands 2002. Slide Seminar 9, "Unusual Head and Neck Lesions". Case 6
32. Brandwein MS, Rothstein A, Lawson W, Bodian C, Urken ML (1997) Sinonasal melanoma. A clinicopathologic study of 25 cases and literature meta-analysis. Arch Otolaryngol Head Neck Surg 123:290–296
33. Brarsman FA (1980) The median nasal sinus and dermoid cyst. Arch Otorhinolaryngol 226:107–113
34. Brook I, Frazier EH (2004) Microbiology of recurrent acute rhinosinusitis. Laryngoscope 114:129–131
35. Buchwald C, Franzmann MB, Jacobsen GK, Lindeberg H (1995) Human papillomavirus (HPV) in sinonasal papillomas: a study of 78 cases using in situ hybridization and the polymerase chain reaction. Laryngoscope 105:66–71
36. Buob D, Wacrenier A, Chevalier D, Aubert S, Quinchon JF, Gosselin B, Leroy X (2003) Schwannoma of the sinonasal tract: a clinicopathologic and immunohistochemical study of 5 cases. Arch Pathol Lab Med 127:1196–1199
37. Callender TA, Weber RS, Janjan N, Benjamin R, Zaher M, Wolf P, el-Naggar A (1995) Rhabdomyosarcoma of the nose and paranasal sinuses in adults and children. Otolaryngol Head Neck Surg 112:252–257
38. Campo E, Cardesa A, Alos L, Palacin A, Cobarro J, Traserra J, Montserrat E (1991) Non-Hodgkin's lymphomas of nasal cavity and paranasal sinuses. An immunohistochemical study. Am J Clin Pathol 96:184–190
39. Cardesa A (1998) Peripheral primitive neuroectodermal tumour, left maxillary sinus. XXII International Congress of the International Academy of Pathology. Nice. France 1998. Slide Seminar 18, "Head and Neck Pathology". Case 12
40. Cardesa A (1998) Sinonasal salivary duct carcinoma metastatic to right cervical lymph nodes. XXII International Congress of the International Academy of Pathology. Nice. France 1998. Slide Seminar 18, "Head and Neck Pathology". Case 6
41. Cardesa A, Alos L (2002) Special tumours of the head and neck region: characterization of undifferentiated sinonasal tumours. Histopathology 41 [Suppl 2]:473–477
42. Cardesa A, Alos LL, Bombi JA, Palacin A, Traserra J (1991) Relative frequency and diagnoses of sinonasal malignant melanoma (SNMM). Lab Invest 64:63A
43. Cardesa A, Bombi JA, Alos L (1993) The classification of tumours of the minor salivary glands. Arquivos de Patologia, Univ. Coimbra, Portugal 25:75–85
44. Cardesa A, Pour P, Haas H, Althoff J, Mohr U (1976) Histogenesis of tumors from the nasal cavities induced by diethylnitrosamine. Cancer 37:346–355
45. Carney ME, O'Reilly RC, Sholevar B et al. (1995) Expression of the human Achaete-scute 1 gene in olfactory neuroblastoma (esthesioneuroblastoma). J Neurooncol 26:35–43
46. Castro EB, Lewis JS, Strong EW (1973) Plasmacytoma of paranasal sinuses and nasal cavity. Arch Otolaryngol 97:326–329
47. Cecchi F, Buiatti E, Kriebel D, Nastasi L, Santucci M (1980) Adenocarcinoma of the nose and paranasal sinuses in shoemakers and woodworkers in the province of Florence, Italy (1963–77). Br J Ind Med 37:222–225
48. Cerilli LA, Holst VA, Brandwein MS, Stoler MH, Mills SE (2001) Sinonasal undifferentiated carcinoma. Immunohistochemical profile and lack of EBV association. Am J Surg Pathol 25:156–163
49. Chan JK (1998) Natural killer cell neoplasms. Anat Pathol 3:77–145
50. Chan JK, Ng CS, Lau WH, Lo ST (1987) Most nasal/nasopharyngeal lymphomas are peripheral T-cell neoplasms. Am J Surg Pathol 11:418–429
51. Chaudry MR, Aktar S, Kim DS (1994) Neuroendocrine carcinoma of the ethmoid sinus. Eur Arch Otorhinolaryngol 251:461–463
52. Cheung MM, Chan JK, Lau WH et al. (1998) Primary non-Hodgkin's lymphoma of the nose and nasopharynx: clinical features, tumor immunophenotype, and treatment outcome in 113 patients. J Clin Oncol 16:70–77
53. Choi HS, Anderson PJ (1986) Olfactory neuroblastoma: an immuno-electron microscopic study of S-100 protein-positive cell. J Neuropathol Exp Neurol 45:576–587
54. Christensen WN, Smith RL (1986) Schneiderian papillomas: a clinicopathologic study of 67 cases. Hum Pathol 17:393–400
55. Cohen MA, Batsakis JG (1968) Oncocytic tumors (oncocytomas) of minor salivary glands. Arch Otolaryngol 88:97–99

56. Compagno J, Wong RT (1977) Intranasal mixed tumours (pleomorphic adenomas). A clinicopathologic study of 40 cases. Am J Clin Pathol 68:213–218
57. Coup AJ, Hopper IP (1980) Granulomatous lesions in nasal biopsies. Histopathology 4:293–308
58. Cove H (1994) Melanosis, melanocytic hyperplasia, and primary malignant melanoma of the nasal cavity. Cancer 44:1424–1433
59. Cunningham MJ, Brantley S, Barnes L, Schramm VL (1987) Oncocytic Schneiderian papilloma in a young adult: a rare diagnosis. Otolaryngol Head Neck Surg 97:47–51
60. Da-Quan M, Guang-Yan Y (1987) Tumours of the minor salivary glands. A clinicopathologic study of 243 cases. Acta Otolaryngol (Stockh) 103:325–331
61. Davis JM, Weber AL (1980) Pituitary adenoma presenting as a sphenoid sinus lesion. Ann Otol Rhinol Laryngol 89:883–884
62. Delgado R, Klimstra D, Albores-Saavedra J (1996) Low grade salivary duct carcinoma. A distinctive variant with low grade histology and a predominant intraductal growth pattern. Cancer 78:958–967
63. Denoyelle F, Ducroz V, Roger G, Garabedian EN (1997) Nasal dermoid sinus cysts in children. Laryngoscope 107:795–800
64. Devgan BK, Devgan M, Gross CW (1978) Teratocarcinoma of the ethmoid sinus: review of literature plus a new case report. Otolaryngol Head Neck Surg 86:689–695
65. Drier JK, Swanson PE, Cherwitz DL, Wick MR (1987) S100 protein immunoreactivity in poorly differentiated carcinomas. Immunohistochemical comparison with malignant melanoma. Arch Pathol Lab Med 111:447–452
66. Dunand VA, Hammer SM, Rossi R, Poulin M, Albrecht MA, Doweiko JP, DeGirolami PC, Coakley E, Piessens E, Wanke CA (1997) Parasitic sinusitis and otitis in patients infected with human immunodeficiency virus: report of five cases and review. Clin Infect Dis 25:267–272
67. Dykewicz MS (2003) 7. Rhinitis and sinusitis. J Allergy Clin Immunol 111:S520–S529
68. Eden BV, Debo RF, Larner JM et al. (1994) Esthesioneuroblastoma. Long term outcome and patterns of failure – the University of Virginia experience. Cancer 73:2556–2562
69. El-Barbary AE-S, Yassin A, Fouad H, Shennawy ME (1976) Histopathological and histochemical studies in atrophic rhinitis. J Laryngol Otol 84:1103–1111

69a. El-Mofty SK, Lu DW (2005) Prevalence of high-risk human papillomavirus DNA in non-keratinising (cylindrical cell) carcinoma of the sinonasal tract. A distinct clinicopathologic and molecular disease entity. Am J Surg Pathol 29:1367–1372

70. Elkon D, Hightower SI, Lim ML, Cantrell RW, Constable WC (1979) Esthesioneuroblastoma. Cancer 44:1087–1094
71. Fang SY, Shen CL (1998) Neuropeptide innervation and neuroendocrine cells in allergic rhinitis and chronic hypertrophic rhinitis. Clin Exp Allergy 28:228–232
72. Fellbaum C, Hansmann ML, Lennert K (1989) Malignant lymphomas of the nasal cavity and paranasal sinuses. Virchows Archiv A Pathol Anat Histopathol 414:399–405
73. Ferguson BJ (2000) Mucormycosis of the nose and paranasal sinuses. Otolaryngol Clin North Am 33:349–365
74. Fernandez PL, Cardesa A, Alos L (1995) Malignant melanoma of the sinonasal tract. Check Sample. APII. Am J Clin Pathol 19:45–58
75. Fernandez PL, Cardesa A, Alos L, Pinto J, Traserra J (1995) Sinonasal teratocarcinosarcoma: an unusual neoplasm. Pathol Res Pract 191:166–171
76. Fernandez PL, Cardesa A, Bombi JA, Palacin A, Traserra J (1993) Malignant sinonasal epithelioid schwannoma. Virchows Arch 423:401–405
77. Ferry JA, Sklar J, Zukerberg RL, Harris NL (1991) Nasal lymphoma. A clinicopathologic study with immunophenotypic and genotypic analysis. Am J Surg Pathol 15:268–279
78. Franchi A, Gallo O, Santucci M (1999) Clinical relevance of the histological classification of sinonasal intestinal-type adenocarcinomas. Hum Pathol 30:1140–1145
79. Franchi A, Massi D, Palomba A, Biancalani M, Santucci M (2004) CDX-2, cytokeratin 7 and cytokeratin 20 immunohistochemical expression in the differential diagnosis of primary adenocarcinomas of the sinonasal tract. Virchows Arch 445:63–67
80. Franchi A, Moroni M, Massi D, Paglierani M, Santucci M (2002) Sinonasal undifferentiated carcinoma, nasopharyngeal-type undifferentiated carcinoma, and keratinizing and nonkeratinizing squamous cell carcinoma express different cytokeratin patterns. Am J Surg Pathol 26:1597–1604
81. Franquemont DW, Fechner RE, Mills SE (1991) Histologic classification of sinonasal intestinal-type adenocarcinoma. Am J Surg Pathol 15:368–375
82. Franquemont DW, Mills SE (1991) Sinonasal malignant melanoma. A clinicopathologic and immunohistochemical study of 14 cases. Am J Clin Pathol 96:689–697
83. Freedman HM, DeSanto LW, Devine KD, Weiland LH (1973) Malignant melanoma of the nasal cavity and paranasal sinuses. Arch Otolaryngol 97:322–325
84. Friedmann I, Osborn DA (1982) Carcinoma of the surface epithelium (including ameloblastoma). In: Friedmann I, Osborn D (eds) Pathology of granulomas and neoplasms of the nose and paranasal sinuses. Churchill Livingstone, Edinburgh, pp 118–132
85. Frierson HF Jr, Innes DJ Jr, Mills SE, Wick M (1989) Immunophenotypic analysis of sinonasal non-Hodgkin's lymphomas. Human Pathol 20:636–642
86. Frierson HF, Mills SE, Fechner RE, Taxy JB, Levine PA (1986) Sinonasal undifferentiated carcinoma. An aggressive neoplasm derived from Schneiderian epithelium and distinct from olfactory neuroblastoma. Am J Surg Pathol 10:771–779
87. Frierson HF Jr, Ross GW, Mills SE, Frankfurter A (1990) Olfactory neuroblastoma. Additional immunohistochemical characterization. Am J Surg Pathol 94:547–553
88. Frodel JL, Larrabee WF, Raisis J (1989) The nasal dermoid. Head Neck Surg 101:392–396
89. Fu YS, Hoover L, Franklin M, Cheng L, Stoler MH (1992) Human papillomavirus identified by nucleic acid hybridization in concomitant nasal and genital papillomas. Laryngoscope 102:1014–1019
90. Fu YS, Perzin KH (1974) Non-epithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx: a clinicopathologic study. I. General features and vascular tumors. Cancer 33:1275–1288
91. Fu YS, Perzin KH (1975) Nonepithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx: a clinicopathologic study. IV. Smooth muscle tumors (leiomyoma, leiomyosarcoma) Cancer 35:1300–1308
92. Gaal K, Sun NCJ, Hernandez AM, Arber DA (2000) Sinonasal NK/T-cell lymphomas in the United States. Am J Surg Pathol 24:1511–1517
93. Gadeberg CC, Hjelm-Hansen M, Sögaard H et al. (1984) Malignant tumors of the paranasal sinuses and nasal cavity. A series of 180 patients. Acta Radiol Oncol 23:181–187
94. Gerughty RM, Hennigar GR, Brown FM (1984) Adenosquamous carcinoma of the nasal, oral and laryngeal cavities. A clinicopathologic survey of ten cases. Cancer 22:1140–1155
95. Ghamrawi KAE, Glennie JM (1974) The value of radiotherapy in the management of malignant melanoma of the nasal cavity. J Laryngol Otol 88:71–75
96. Gnepp DR, Henley J, Weiss S, Heffner D (1996) Desmoid fibromatosis of the sinonasal tract and nasopharynx. A clinicopathologic study of 25 cases. Cancer 78:2572–2579
97. Goren AD, Harley N, Eisenbud L, Levin S, Cohen N (1980) Clinical and radiobiologic features of Thorotrast-induced carcinoma of the maxillary sinus. A case report. Oral Surg Oral Med Oral Pathol 49:237–242
98. Gosavi DK, Moidekar AT (1978) Chemodectoma of the nose and sphenoid sinus. J Laryngol Otol 92:813–816
99. Gouldesbrough DR, Martin-Hirsch DP, Lannigan F (1992) Intranasal malignant melanoma arising in an inverted papilloma. Histopathology 20:523–526
100. Guarisco JL, Butcher RB (1990) Congenital cystic teratoma of the maxillary sinus. Otolaryngol Head Neck Surg 103:1035–1038

101. Gupta A, Seiden AM (2003) Nasal leprosy: case study. Otolaryngol Head Neck Surg 129:608–610
102. Hadfield EH, Macbeth RG (1971) Adenocarcinoma of ethmoids in furniture workers. Ann Otol Rhinol Laryngol 80:699–703
103. Handler SD, Ward PH (1979) Oncocytoma of the maxillary sinus. Laryngoscope 69:372–376
104. Hanna GS, Ali MH (1987) Verrucous carcinoma of the nasal septum. J Laryngol Otol 101:184–187
105. Harbo G, Grau C, Bundgaard T, Overgaard M, Elbrond O, Sogaard H, Overgaard J (1997) Cancer of the nasal cavity and paranasal sinuses. A clinico-pathological study of 277 patients. Acta Oncol 36:45–50
106. Hardy G (1957) The choanal polyp. Ann Otol Laryngol Rhinol 66:306–326
107. Harrison DFN (1976) Malignant melanomata arising in the nasal mucous membrane. J Laryngol Otol 90:993–1005
108. Hasegawa SL, Mentzel T, Fletcher CD (1997) Schwannomas of the sinonasal tract and nasopharynx. Mod Pathol 10:777–784
109. Heffner DK (1983) Problems in pediatric otorhinolaryngic pathology. I. Sinonasal and nasopharyngeal tumors and masses with myxoid features. Int J Pediatr Otorhinolaryngol 5:77–91
110. Heffner DK (1991) Sinonasal and laryngeal salivary gland lesions. In: Ellis GL, Auclair PL, Gnepp DR (eds) Surgical pathology of salivary glands. Saunders, Philadelphia, pp 544–559
111. Heffner DK, Gnepp DR (1992) Sinonasal fibrosarcomas, malignant schwannomas, and "Triton" tumors. A clinicopathologic study of 67 cases. Cancer 70:1089–1101
112. Heffner DK, Hyams VJ (1984) Teratocarcinosarcoma (malignant teratoma?) of the nasal cavity and paranasal sinuses. Cancer 53:2140–215
113. Heffner DK, Hyams VJ, Hauck KW, Lingeman C (1982) Low-grade adenocarcinoma of the nasal cavity and paranasal sinuses. Cancer 50:312–322
114. Helliwell TR, Yeoh LH, Stell PM (1986) Anaplastic carcinoma of the nose and paranasal sinuses. Light microscopy, immunohistochemistry, and clinical correlation. Cancer 58:2038–2045
115. Hellquist HB (1996) Nasal polyps update. Histopathology. Allergy Asthma Proc 17:237–242
116. Herrmann BW, Sotelo-Avila C, Eisenbeis JF (2003) Pediatric sinonasal rhabdomyosarcoma: three cases and a review of the literature. Am J Otolaryngol 24:174–180
117. Hillstrom RP, Zarbo RJ, Jacobs JR (1990) Nerve sheath tumors of the paranasal sinuses: electron microscopy and histopathologic diagnosis. Otolaryngol Head Neck Surg 102:257–263
118. Ho KL (1980) Primary meningioma of the nasal cavity and paranasal sinuses. Cancer 46:1442–1447
119. Huang HY, Antonescu CR (2003) Sinonasal smooth muscle cell tumors: a clinicopathologic and immunohistochemical analysis of 12 cases with emphasis on the low-grade end of the spectrum. Arch Pathol Lab Med 127:297–304
120. Hwang HC, Mills SE, Patterson K, Gown AM (1998) Expression of androgen receptors in nasopharyngeal angiofibroma: an immunohistochemical study of 24 cases. Mod Pathol 11:1122–1126
121. Hyams VJ (1971) Papillomas of the nasal cavity and paranasal sinuses. A clinicopathologic study of 315 cases. Ann Otol Rhinol Laryngol 80:192–206
122. Hyams VJ, Batsakis JG, Michaels L (1988) Tumors of the upper respiratory tract and ear. In: Atlas of Tumor Pathology, 2nd series. Fascicle 25. Armed Forces Institute of Pathology, Washington, D.C.
123. Imbus HR, Dyson WL (1987) A review of nasal cancer in furniture manufacturing and woodworking in North Carolina, the United States, and other countries. J Occup Med 29:734–740
124. Ironside P, Matthews J (1975) Adenocarcinoma of the nose and paranasal sinuses in woodworkers in the state of Victoria, Australia. Cancer 36:1115–1124
125. Jacobsson M, Petruson B, Svendsen P, Berthelsen B (1988) Juvenile nasopharyngeal angiofibroma. A report of eighteen cases. Acta Otolaryngol 105:132–139
126. Jarvi O (1945) Heterotopic tumors with an intestinal mucous membrane structure in the nasal cavity. Acta Otolaryngol 33:471–85
127. Jeng YM, Sung MT, Fang CL, Huang HY, Mao TL, Cheng W, Hsiao CH (2002) Sinonasal undifferentiated carcinoma and nasopharyngeal-type undifferentiated carcinoma. Two clinically, biologically, and histopathologically distinct entities. Am J Surg Pathol 26:371–376
128. Judd R, Zaki SR, Coffield LM, Evatt BL (1991) Sinonasal papillomas and human papillomavirus: human papillomavirus 11 detected in fungiform schneiderian papillomas by in situ hybridization and the polymerase chain reaction. Hum Pathol 22:550–556
129. Kadish S, Goodman M, Wang CC (1976) Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer 37:1571–1576
130. Kagan AR, Nussbaum H, Rao A, Chan P, Gilbert H, Hintz B, Ryoo M, Miles J, Rice D (1981) The management of carcinoma of the nasal vestibule. Head Neck Surg 4:125–128
131. Kahn LB (1974) Esthesioneuroblastoma. A light and electron microscopic study. Hum Pathol 5:364–371
132. Kameya T, Shimosato Y, Adachi I, Abe K, Ebihara S, Ono I (1980) Neuroendocrine carcinoma of the paranasal sinus. A morphological and endocrinological study. Cancer 45:330–339
133. Kapadia SB (1985) Hematologic diseases: malignant lymphomas, leukemias, plasma cell dyscrasias, histiocytosis X, and reactive lymph node lesions. In: Barnes L (ed) Surgical pathology of the head and neck, vol 2. Dekker, New York
134. Kapadia SB, Barnes L, Deutsch M (1981) Non-Hodgkin's lymphoma of the nose and paranasal sinuses: a study of 17 cases. Head Neck Surg 3:490–499
135. Kapadia SB, Barnes L, Pelzman K, Mirani N, Heffner DK, Bedetti C (1993) Carcinoma ex oncocytic Schneiderian (cylindrical cell) papilloma. Am J Otolaryngol 14:332–338
136. Karma P, Rasanen O, Karja J (1977) Nasal gliomas. A review and report of two cases. Laryngoscope 87:1169–1179
137. Katzenstein AL, Sale SR, Greenberger PA (1983) Pathologic findings in allergic aspergillus sinusitis. A newly recognized form of sinusitis. Am J Surg Pathol 7:439–443
138. Kim ST, Kim CW, Han GC, Park C, Jang IH, Cha HE, Choi G, Lee HM (2001) Malignant triton tumor of the nasal cavity. Head Neck 23:1075–1078
139. Kleinsasser O (1985) Terminal tubulus adenocarcinoma of the nasal seromucous glands. A specific entity. Arch Otorhinolaryngol 241:183–193
140. Kleinsasser O, Schroeder HG (1988) Adenocarcinoma of the inner nose after exposure to wood dust. Morphological findings and relationships between histopathology and clinical behavior in 79 cases. Arch Otorhinolaryngol 245:1–15
141. Klein-Szanto AJ, Boysen M, Reith A (1987) Keratin and involucrin in preneoplastic and neoplastic lesions. Distribution in the nasal mucosa of nickel workers. Arch Pathol Lab Med 111:1057–1061
142. Klintenberg C, Olofsson J, Hellquist H, Sokjer H (1984) Adenocarcinoma of the ethmoid sinuses. A review of 28 cases with special reference to wood dust exposure. Cancer 54:482–488
143. Krespi YP, Kuriloff DB, Aner M (1995) Sarcoidosis of the sinonasal tract: a new staging system. Otolaryngol Head Neck Surg 112:221–227
144. Kuruvilla A, Wenig BM, Humphrey DM, Heffner DK (1990) Leiomyosarcoma of the sinonasal tract. A clinicopathologic study of nine cases. Arch Otolaryngol Head Neck Surg 116:1278–1286
145. Kyriakos M (1977) Myospherulosis of the paranasal sinuses, nose and middle ear. A possible iatrogenic disease. Am J Clin Pathol 67:118–130
146. Larsson LG, Martensson G (1972) Maxillary antral cancers. JAMA 219:342–345
147. Lee BJ, Park HJ, Heo SC (2003) Organized hematoma of the maxillary sinus. Acta Otolaryngol 123:869–872

148. Lewis MG, Martin JAM (1967) Malignant melanoma of the nasal cavity in Ugandan Africans: relationship of ectopic pigmentation. Cancer 20:1699–1705
149. Llombart-Bosch A, Terrier-Lacombe J, Peydro-Olaya A, Contesso G (1989) Peripheral neuroectodermal sarcoma of soft tissue (peripheral neuroepithelioma): a pathologic study of ten cases with differential diagnosis regarding other small, round-cell sarcomas. Hum Pathol 20:273–280
150. Lloreta J, Serrano S, Corominas JM, Ferrer-Padro E (1995) Polymorphous low-grade adenocarcinoma arising in the nasal cavities with an associated undifferentiated carcinoma. Ultrastruct Pathol 19:365–370
151. Lloreta-Trull J, Mackay B, Troncoso P, Ribalta-Farres T, Smith T, Khorana S (1992) Neuroendocrine tumors of the nasal cavity: an ultrastructural study of 24 cases. Ultrstruct Pathol 16: 165–175
152. Lloyd RV, Chandler WF, Kovaks K, Ryan N (1986) Ectopic pituitary adenomas with normal anterior pituitary glands. Am J Surg Pathol 108:546–552
153. Lohuis PJ, Lipovsky MM, Hoepelman AI, Hordijk GJ, Huizing EH (1997) Leishmania braziliensis presenting as a granulomatous lesion of the nasal septum mucosa. J Laryngol Otol 111:973–975
154. Loree TR, Mullins AP, Spellman J, North JH Jr, Hicks WL Jr (1999) Head and neck mucosal melanoma: a 32-year review. Ear Nose Throat J 78:372–375
155. Luce D, Gerin M, Leclerc A, Morcet JF, Brugere J, Goldberg M (1993) Sinonasal cancer and occupational exposure to formaldehyde and other substances. Int J Cancer 53:224–231
156. Luna MA (1995) Critical commentary to "Sino nasal teratocarcinosarcoma". Pathol Res Pract 191:172
157. Lund V (1982) Malignant melanoma of the nasal cavity and paranasal sinuses. J Laryngol Otol 96:347–355
158. Lund VJ, Milroy CM (1991) Fronto-ethmoidal mucoceles: a histopathological analysis. J Laryngol Otol 105:921–923
159. Mackay B, Luna MA, Butler JJ (1976) Adult neuroblastoma. Electronmicroscopic observations in nine cases. Cancer 37:1334–1351
160. Majumdar B, Kent S (1983) Malignant neoplasms of the nose and paranasal sinuses. A survey of cases treated in a regional centre. Clin Otolaryngol 8:97–102
161. Makannavar JH, Chavan SS (2001) Rhinosporidiosis. A clinicopathological study of 34 cases. Indian J Pathol Microbiol 44:17–21
162. Manivel C, Wick MR, Dehner LP (1986) Transitional (cylindric) cell carcinoma with endodermal sinus tumor-like features of the nasopharynx and paranasal sinuses. Clinicopathologic and immunohistochemical study of two cases. Arch Pathol Lab Med 110:198–202
163. Mannan AA, Singh MK, Bahadur S, Hatimota P, Sharma MC (2003) Solitary malignant schwannoma of the nasal cavity and paranasal sinuses: report of two rare cases. Ear Nose Throat J 82:634–646
164. Marks SC, Upadhyay S, Crane L (1996) Cytomegalovirus sinusitis. A new manifestation of AIDS. Arch Otolaryngol Head Neck Surg 122:789–791
165. McDonald TJ, DeRemee RA, Kern EB, Harrison EG Jr (1974) Nasal manifestations of Wegener's granulomatosis. Laryngoscope 84:2101–2112
166. McKinney CD, Mills SE, Franquemont DW (1995) Sinonasal intestinal-type adenocarcinoma. Immunohistochemical profile and comparison with colonic adenocarcinoma. Mod Pathol 8:421–426
167. Mendenhall WM, Stringer SP, Cassisi NJ, Mendenhall NP (1999) Squamous cell carcinoma of the nasal vestibule. Head Neck 21:385–393
168. Mentzel T, Bainbridge TC, Katenkamp D (1997) Solitary fibrous tumour: clinicopathological, immunohistochemical, and ultrastructural analysis of 12 cases arising in soft tissues, nasal cavity and nasopharynx, urinary bladder and prostate. Virchows Arch 430:445–453
169. Mesara BW, Batsakis JG (1966) Glandular tumors of the upper respiratory tract. A clinicopathologic assessment. Arch Surg 92:872–878
170. Meyer RD, Gaultier CR, Yamashita JT, Babapour R, Pitchon HE, Wolfe PR (1994) Fungal sinusitis in patients with AIDS: report of 4 cases and review of the literature. Medicine (Baltimore) 73:69–78
171. Michaels L, Hellquist HB (2001) Ear, nose and throat histopathology. Springer, Berlin Heidelberg New York
172. Michaels L, Lloyd G, Phelps P (2000) Origin and spread of allergic fungal disease of the nose and paranasal sinuses. Clin Otolaryngol 25:518–525
173. Michaels L, Young M (1995) Histogenesis of papillomas of the nose and paranasal sinuses. Arch Pathol Lab Med 119:821–826
174. Mills SE, Fechner RE, Cantrell RW (1982) Aggressive sinonasal lesion resembling normal intestinal mucosa. Am J Surg Pathol 6:803–809
175. Mills SE, Frierson HF (1985) Olfactory neuroblastoma. A clinicopathologic study of 21 cases. Am J Surg Pathol 9:317–327
176. Mills SE, Gaffey MJ, Frierson HF (2000) Tumors of the upper aerodigestive tract and ear. Atlas of tumor pathology. Third Series. Fascicle 26. Armed Forces Institute of Pathology. Washington D.C.
177. Min YG, Shin JS, Choi SH, Chi JG, Yoon CJ (1995) Primary ciliary dyskinesia: ultrastructural defects and clinical features. Rhinology 33:189–193
178. Moore EJ, Kern EB (2001) Atrophic rhinitis: a review of 242 cases. Am J Rhinol 15:355–361
179. Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, Quast LM (1993) Esthesioneuroblastoma: prognosis and management. Neurosurgery 32:706–715
180. Mufarrij AA, Busaba NY, Zaytoun GM, Gallo GR, Feiner HD (1990) Primary localized amyloidosis of the nose and paranasal sinuses. A case report with immunohistochemical observations and a review of the literature. Am J Surg Pathol 14:379–383
181. Nakashima T, Kimmelman CP, Snow JB Jr (1984) Structure of human fetal and adult olfactory neuroepithelium. Arch Otolaryngol 110:641–646
182. Nakashima T, Kimmelman CP, Snow JB Jr (1985) Olfactory marker protein in the human olfactory pathway. Arch Otolaryngol 111:294–297
183. Nakayama M, Wenig BM, Heffner DK (1995) Atypical stromal cells in inflammatory nasal polyps: immunohistochemical and ultrastructural analysis in defining histogenesis. Laryngoscope 105:127–134
184. Natvig K, Larsen TE (1978) Mucocele of the paranasal sinuses. A retrospective clinical and histological study. J Laryngol Otol 92:1075–1082
185. Navarrete ML, Quesada P, Pellicer M, Ruiz C (1991) Extramedullary nasal plasmacytoma. J Laryngol Otol 105:41–43
186. Ng HK, Poon WS, Poon CY, South JR (1988) Intracranial olfactory neuroblastoma mimicking carcinoma: report of two cases. Histopathology 12:393–403
187. Nguyen QA, Gibbs PM, Rice DH (1995) Malignant nasal paraganglioma: a case report and review of the literature. Otolaryngol Head Neck Surg 113:157–161
188. O'Connor GT Jr, Drake CR, Johns ME, Cail WS, Winn HR, Niskanen E (1985) Treatment of advanced esthesioneuroblastoma with high-dose chemotherapy and autologous bone marrow transplantation. A case report. Cancer 55:347–349
189. Oppenheimer EH, Rosenstein BJ (1979) Differential pathology of nasal polyps in cystic fibrosis and atopy. Lab Invest 40:455–449
190. Ordoñez NG, Batsakis JG (1986) Acinic cell carcinoma of the nasal cavity: electron-optic and immunohistochemical observations. J Laryngol Otol 100:345–349
191. Ordóñez NG, Mackay B (1993) Neuroendocrine tumors of the nasal cavity. Pathol Annu 28:77–111
192. Orvidas LJ, Lewis JE, Olsen KD, Weiner JS (1999) Intranasal verrucous carcinoma; relationship to inverting papilloma and human papillomavirus. Laryngoscope 109:371–375
193. Osborn DA (1956) Transitional cell growths of the upper respiratory tract. J Laryngol Otol 70:574–587
194. Osborn DA (1970) Nature and behavior of transitional tumors in the upper respiratory tract. Cancer 25:50–60

195. Pai SA, Naresh KN, Masih K, Ramarao C, Borges AM (1998) Teratocarcinosarcoma of the paranasal sinuses: a clinicopathologic and immunohistochemical study. Hum Pathol 29:718–722
196. Patterson K, Kapur S, Chandra RS (1986) "Nasal gliomas" and related brain heterotopias: a pathologist's perspective. Pediatr Pathol 5:353–362
197. Patuano E, Carrat X, Drouet Y, Barnabe D, Vincey P, Berthelot B (1993) Mucocutaneous leishmaniasis in otorhinolaryngology. Ann Otolaryngol Chir Cervicofac 110:415–419
198. Paugh DR, Sullivan MJ(1990) Myospherulosis of the paranasal sinuses. Otolaryngol Head Neck Surg 103:117–119
199. Perez-Ordoñez B, Caruana SM, Huvos AG, Shah JP (1998) Small cell neuroendocrine carcinoma of the of the nasal cavity and paranasal sinuses. Hum Pathol 29:826–832
200. Perzin KH, Cantor JO, Johannessen JV (1981) Acinic cell carcinoma arising in the nasal cavity: report of a case with ultrastructural observations. Cancer 47:1818–1822
201. Perzin KH, Fu YS (1980) Non-epithelial tumors of the nasal cavity, paranasal sinuses and nasopharynx: a clinico-pathologic study. XI. Fibrous histiocytomas. Cancer 45:2616–2626
202. Perzin KH, Panyu H, Wechter S (1982) Nonepithelial tumors of the nasal cavity, paranasal sinuses and nasopharynx. A clinicopathologic study. XII. Schwann cell tumors (neurilemoma neurofibroma, malignant schwannoma). Cancer 50:2193–2202
203. Perzin KH, Pushparaj N (1984) Nonepithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx. A clinicopathologic study. XIII. Meningiomas. Cancer 54:1860–1869
204. Phillips PP, Gustafson RO, Facer GW (1990) The clinical behavior of inverting papilloma of the nose and paranasal sinuses; report of 112 cases and review of the literature. Laryngoscope 100:468–469
205. Piscioli F, Aldovini D, Bondi A, Eusebi V (1984) Squamous cell carcinoma with sarcoma-like stroma of the nose and paranasal sinuses: report of two cases. Histopathology 8:633–639
206. Pitman KT, Prokopakis EP, Aydogan B, Segas J, Carrau RL, Snyderman CH,Janecka IP, Hanna E, D'Amico F, Johnson JT (1999) The role of skull base surgery for the treatment of adenoid cystic carcinoma of the sinonasal tract. Head Neck 21:402–407
207. Prasad ML, Jungbluth AA, Iversen K, Huvos AG, Busam KL (2001) Expression of melanocytic differentiation markers in malignant melanomas of the oral and sinonasal mucosa. Am J Surg Pathol 25:782–787
208. Raychowdhuri RN (1965) Oat cell carcinoma and paranasal sinuses. J Laryngol Otol 79:253–255
209. Regauer S, Anderhuber W, Richtig E, Schachenreiter J, Ott A, Beham A (1998) Primary mucosal melanomas of the nasal cavity and paranasal sinuses. A clinicopathologic analysis of 14 cases. APMIS 106:403–404
210. Rejowski JE, Campanella RS, Block LJ (1982) Small cell carcinoma of the nose and paranasal sinuses. Otolaryngol Head Neck Surg 90:516–517
211. Ridolfi RL, Liberman PH, Erlandson RA, Moore OS (1977) Schneiderian papillomas; a clinicopathologic study of 30 cases. Am J Surg Pathol 1:43–53
212. Ringertz N (1938) Pathology of malignant tumours arising in the nasal and paranasal cavities and maxilla. Acta Otolaryngol Suppl 27:31–42
213. Robbins KT, Fuller LM, Vlasak M et al. (1985) Primary lymphomas of the nasal cavity and paranasal sinuses. Cancer 56:814–819
214. Roberts PF, McCann BG (1985) Eosinophilic angiocentric fibrosis of the upper respiratory tract: a mucosal variant of granuloma faciale? A report of three cases. Histopathology 9:1217–1225
215. Robin PE, Powell DJ (1980) Regional node involvement and distant metastases in carcinoma of the nasal cavity and paranasal sinuses. J Laryngol Otol 94:301–309
216. Robin PE, Powell DJ, Stassbie JM (1979) Carcinoma of the nasal cavity and paranasal sinuses: incidence and presentation of different histological types. Clin Otolaryngol 4:431–456
217. Rosai J (1978) The nature of myospherulosis of the upper respiratory tract. Am J Clin Pathol 69:475–481
218. Rousch GC (1979) Epidemiology of cancer of the nose and paranasal sinuses: current concepts. Head Neck Surg 2:3–11
219. Sadler TW (1985) Langman's medical embryology, 5th edn. Williams & Wilkins, Baltimore
220. Sanchez-Casis G, Devine KD, Weiland LH (1971) Nasal adenocarcinomas that closely simulate colonic carcinomas. Cancer 28:714–729
221. Sarkar FH, Visscher DW, Kintanar EB, Zarbo RJ, Crissman JD (1992) Sinonasal schneiderian papillomas: human papillomavirus typing by polymerase chain reaction. Mod Pathol 5:329–332
222. Schmid KO, Aubock L, Albegger K (1979) Endocrine-amphicrine enteric carcinoma of the nasal mucosa. Virchows Arch A Pathol Anat Histol 383:329–343
223. Schwartz S, Thiel E (1997) Clinical presentation of invasive aspergillosis. Mycoses 40 [Suppl 2]:21–24
224. Seifert G (1991) WHO histological typing of salivary gland tumours. Springer, Berlin Heidelberg New York
225. Seyer BA, Grist W, Muller S (2002) Aggressive destructive midfacial lesion from cocaine abuse. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 94:465–470
226. Shanmugaratnam K (1991) WHO histological typing of tumours of the upper respiratory tract and ear. Springer, Berlin Heidelberg New York
227. Shanmugaratnam K, Kunaratnam N, Chia KB, Chiang GS, Sinniah R (1983) Teratoid carcinosarcoma of the paranasal sinuses. Pathology 15:413–419
228. Shimada K, Kobayashi S, Yamadori I, Ohmori M (1988) Myospherulosis in Japan. A report of two cases and an immunohistochemical investigation. Am J Surg Pathol 12:427–432
229. Silva EG, Butler JJ, Mackay B, Goepfert H (1982) Neuroblastomas and neuroendocrine carcinomas of the nasal cavity. A proposed new classification. Cancer 50:2388–2405
230. Sindwani R, Cohen JT, Pilch BZ, Metson RB (2003) Myospherulosis following sinus surgery: pathological curiosity or important clinical entity? Laryngoscope 113:1123–1127
231. Singhal SK, Dass A, Mohan H, Venkataramana Y (2002) Primary nasal tuberculosis. J Otolaryngol 31:60–62
232. Siniluoto TM, Luotonen JP, Tikkakoski TA, Leinonen AS, Jokinen KE (1993) Value of pre-operative embolization in surgery for nasopharyngeal angiofibroma. J Laryngol Otol 107:514–521
233. Siu LL, Chan V, Chan JK, Wong KF, Liang R, Kwong YL (2000) Consistent patterns of allelic loss in natural killer cell lymphoma. Am J Pathol 157:1803–1809
234. Skalova A, Cardesa A, Leivo I, Pfaltz M, Ryska A, Simpson R, Michal M (2003) Sinonasal tubulopapillary low grade adenocarcinoma. Histopathological, immunohistochemical and ultrastructural features of a poorly recognized entity. Virchows Arch 443:152–158
235. Smith CJ, Echevarria R, McLelland CA (1974) Pseudosarcomatous changes in antrochoanal polyps. Arch Otolaryngol 99:228–230
236. Smith O, Gullane PJ (1987) Inverting papilloma of the nose: analysis of 48 patients. J Otolaryngol 16:154–156
237. Sobin LH, Wittekind C (2002) UICC TNM classification of malignant tumours, 6th edn. Wiley-Liss, New York
238. Sorensen PH, Liu XF, Delattre O et al. (1993) Reverse transcriptase PCR amplification of EWS/FLI-1 fusion transcripts as a diagnostic test for peripheral primitive neuroectodermal tumors of childhood. Diagn Mol Pathol 2:147–157
239. Spiro RH, Koss LG, Hajdu SI, Strong EW (1973) Tumors of minor salivary gland origin: a clinicopathologic study of 492 cases. Cancer 31:117–129
240. Stammberger H (1983) Neue Aspekte zur Genese des invertierten Papilloms. Laryngol Rhinol Otol (Stuttg) 62:249–255
241. Stewart FM, Lazarus HM, Levine PA, Stewart KA, Tabbara IA, Spaulding CA (1989) High-dose chemotherapy and autologous marrow transplantation for esthesioneuroblastoma and sinonasal undifferentiated carcinoma. Am J Clin Oncol 12:217–221

242. Stierna P, Carlsoo B (1990) Histopathological observations in chronic maxillary sinusitis. Acta Otolaryngol 110:450–458
243. Sunderman FW Jr, Morgan LG, Andersen A, Ashley D, Forouhar FA (1989) Histopathology of sinonasal and lung cancers in nickel refinery workers. Ann Clin Lab Sci 19:44–50
244. Takeshita H, Miwa T, Furukawa M (2002) Osteocartilaginous differentiation of mucosal melanoma in the sinonasal cavity. Ann Otol Rhinol Laryngol 111:1112–1115
245. Taxy JB (1997) Squamous carcinoma of the nasal vestibule. An analysis of five cases and literature review. Am J Clin Pathol 107:698–703
246. Taxy JB, Bharani NK, Mills SE, Frierson HF Jr, Gould VE (1986) The spectrum of olfactory neural tumors. A light-microscopic, immunohistochemical and ultrastructural analysis. Am J Surg Pathol 10:687–705
247. Taxy JB, Hidvegi DF (1977) Olfactory neuroblastoma: an ultrastructural study. Cancer 39:131–138
248. Thompson LD, Heffner DK (2001) Sinonasal tract eosinophilic angiocentric fibrosis. A report of three cases. Am J Clin Pathol 115:243–248
249. Thompson LD, Miettinen M, Wenig BM (2003) Sinonasal-type hemangiopericytoma: a clinicopathologic and immunophenotypic analysis of 104 cases showing perivascular myoid differentiation. Am J Surg Pathol 27:737–749
250. Thompson LD, Wieneke JA, Miettinen M (2003) Sinonasal tract and nasopharyngeal melanomas: a clinicopathologic study of 115 cases with a proposed staging system. Am J Surg Pathol 27:594–611
251. Topilko A, Zakrzewski A, Pichard E, Viron A (1984) Ultrastructural cytochemistry of intranuclear dense granules in nasopharyngeal angiofibroma. Ultrastruct Pathol 6:221–228
252. Torjussen W, Haug FM, Andersen I (1978) Concentration and distribution of heavy metals in nasal mucosa of nickel-exposed workers and of controls, studied with atomic absorption spectrophotometric analysis and with Timm's sulphide silver method. Acta Otolaryngol 86:449–463
253. Torjusen W, Solberg LA, Hogetvit AC (1979) Histopathologic changes of the nasal mucosa in nickel workers. A pilot study. Cancer 44:963–974
254. Torske KR, Benson GS, Warnock G (2001) Dermoid cyst of the maxillary sinus. Ann Diagn Pathol 5:172–176
255. Tran I, Sidrys J, Horton D et al. (1989) Malignant salivary gland tumors of the paranasal sinuses and nasal cavity. The UCLA experience. Am J Clin Oncol 12:387–392
256. Trapp TK, Fu YS, Calcaterra TC (1987) Melanoma of the nasal and paranasal sinus mucosa. Head Neck Surg 113:1086–1089
257. Trojanowski JQ, Lee V, Pillsbury N, Lee S (1982) Neuronal origin of human esthesioneuroblastoma demonstrated with anti-neurofilament monoclonal antibodies. N Engl J Med 307:159–161
258. Tsikoudas A, Martin-Hirsch DP, Woodhead CJ (2001) Primary sinonasal amyloidosis. J Laryngol Otol 115:55–56
259. Tufano RP, Mokadam NA, Montone KT Weinstein GS, Chalian AA, Wolf PF, Weber RS (1999) Malignant tumors of the nose and paranasal sinuses: hospital of the University of Pennsylvania experience 1990–1997. Am J Rhinol 13:117–123
260. Turc-Carel C, Aurias A, Mugneret F, Lizard S, Sidaner I, Volk C, Thiery JP, Olschwang S, Philip I, Berger MP (1988) Chromosomes in Ewing's sarcoma. I. An evaluation of 85 cases of remarkable consistency of t(11;22)(q24;q12). Cancer Genet Cytogenet 32:229–238
261. Walike JW (1973) Anatomy of the nasal cavities. Otolaryngol Clin North Am 6:609–621
262. Ward BE, Fechner RE, Mills SE (1990) Carcinoma arising in oncocytic Schneiderian papilloma. Am J Surg Pathol 14:364–369
263. Weidner N, Tjoe J (1994) Immunohistochemical profile of monoclonal antibody O13: antibody that recognizes glycoprotein p30/32MIC2 and is useful in diagnosing Ewing's sarcoma and peripheral neuroepithelioma. Am J Surg Pathol 18:486–494
264. Weiss MD, deFies HO, Taxy JB, Braine H (1983) Primary small cell carcinoma of the paranasal sinuses. Arch Otolaryngol 109:341–343
265. Weissler MC, Montgomery WW, Montgomery SK, Turner PA, Joseph MP (1986) Inverted papilloma. Ann Otol Rhinol Laryngol 95:215–221
266. Wenig BM, Heffner DK (1995) Respiratory epithelial adenomatoid hamartomas of the sinonasal tract and nasopharynx: a clinicopathologic study of 31 cases. Ann Otol Rhinol Laryngol 104:639–645
267. Wenig BM, Hyams VJ, Heffner DK (1988) Nasopharyngeal papillary adenocarcinoma. A clinicopathologic study of a low-grade carcinoma. Am J Surg Pathol 12:946–953
267a. World Health Organization Classification of Tumours (2005) Pathology and genetics of tumours of the head and neck. IARC, Lyon
268. Wick MR, Stanley SJ, Swanson PE (1988) Immunohistochemical diagnosis of sinonasal melanoma, carcinoma, and neuroblastoma with monoclonal antibodies HMB-45 and antisynaptophysin. Arch Pathol Lab Med 112:616–620
269. Wieneke JA, Thompson LD, Wenig BM (1999) Basaloid squamous cell carcinoma of the sinonasal tract. Cancer 85:841–854
270. Wilhelmsson B, Hellquist H, Olofsson J, Klintenberg C (1985) Nasal cuboidal metaplasia with dysplasia. Precursor to adenocarcinoma in wood-dust exposed workers? Acta Otolaryngol 99:641–648
271. Winther B, Gwaltney JM Jr, Mygind N, Hendley JO (1998) Viral-induced rhinitis. Am J Rhinol 12:17–20
271a. Wittekind C, Greene FL, Hutter RVP, Klimpfinger M, Sobin LH (2004) UICC TNM atlas. Illustrated guide to the TNM/pTNM classification of malignant tumours. 5th edn. Springer, Berlin
272. Wolff M (1974) Granulomas in nasal mucous membranes following local steroid injections. Am J Clin Pathol 62:775–782
273. Woodson GE, Robbins KT, Michaels L (1985) Inverted papilloma. Considerations in treatment. Arch Otolaryngol 111:806–811
274. Yang YJ, Abraham JL (1997) Undifferentiated carcinoma arising in oncocytic Schneiderian (cylindrical cell) papilloma. J Oral Maxillofac Surg 55:289–294
275. Zak FG, Lawson W (1974) The presence of melanocytes in the nasal cavity. Ann Otol Rhinol Laryngol 83:515–519
276. Zarbo RJ, Crissman JD, Venkat H, Weiss MA (1986) Spindle-cell carcinoma of the upper aerodigestive tract mucosa. Am J Surg Pathol 10:741–753
277. Zarbo RJ, Ricci A, Kowalczyk PD, Kartun RW, Knibbs DR (1985) Intranasal dermal analogue tumor (membranous basal cell adenoma). Arch Otolaryngol 111:333–337
278. Zerris VA, Annino D, Heilman CB (2002) Nasofrontal dermoid sinus cyst: report of two cases. Neurosurgery 51:811–814
279. Zukerberg LR, Rosenberg AE, Randolph G, Pilch BZ, Goodman ML (1991) Solitary fibrous tumor of the nasal cavity and paranasal sinuses. Am J Surg Pathol 15:126–130
280. Zur KB, Brandwein M, Wang B, Som P Gordon R, Urken ML (2002) Primary description of a new entity; renal cell-like carcinoma of the nasal cavity. Van Meegeren in the house of Vermeer. Arch Otolaryngol Head Neck Surg 128:441–447
281. Zurlo JJ, Feuerstein IM, Lebovics R, Lane HC (1992) Sinusitis in HIV-1 infection. Am J Med 93:157–162