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2.1 Introduction

The nasal cavity and paranasal sinuses occupy the top of the upper respiratory tract and form pneumatic spaces connected with the atmosphere. They are located immediately beneath the base of the cranium, where vital structures are harbored. From this region, very much exposed to airborne agents, arise some of the more complex and rare benign and malignant lesions seen in humans, whose difficulties in interpretation make this remarkable territory one of the most challenging in the practice of surgical pathology. Knowledge of the embryology, anatomy, and histology of the nasal cavity and paranasal sinuses is therefore an essential prerequisite for the precise understanding of the pathology of the lesions that develop in this unique region.

2.1.1 Embryology

The midface, or area between the upper lip and forehead, develops between 4 and 8 weeks of gestation [1]. 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, two surface thickenings of the nasal swellings form 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 nares (noses) and, more deeply, the primitive anterior choanae. The medial nasal and frontonasal processes give rise to the nasal septum and maxillary processes, with the exception of the roof [2]. 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 nasal cavity communicates posteriorly with the nasopharynx through the choanae and anteriorly with the nostril. The dilatation formed inside the aperture of each nostril is known as the vestibule. The columnella separates medially both vestibules. The paranasal sinuses are a group of cavities within the corresponding craniofacial bones (maxilla, sphenoid, ethmoid, and frontal) which communicate with the nasal cavities through an ostium.

2.1.2 Anatomy

The nasal cavities are separated by the nasal septum and limited by a roof which is centrally formed by the cribriform plate of the ethmoid (horizontal part), anteriorly by the frontal and nasal bones, and posteriorly by the body of the sphenoid. The floor is formed by the hard palate, which comprises the palatine process of the maxillary bone and the horizontal plate of the palatine bone [2]. The lateral walls have three turbinates or conchae and three horizontal spaces, or meati, 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 sphenoid ethmoid recess, with the openings of the sphenoid and posterior ethmoid sinuses. Each nasal cavity communicates posteriorly with the nasopharynx through the choanae and anteriorly with the nostril. The dilatation formed inside the aperture of each nostril is known as the vestibule. The columnella separates medially both vestibules. The paranasal sinuses are a group of cavities within the corresponding craniofacial bones (maxilla, sphenoid, ethmoid, and frontal) which communicate with the nasal cavities through an ostium.

2.1.3 Histology

The nasal vestibule shares similar histology with the skin. At the level of the limen nasi, the boundary between the osseous and cartilaginous walls of the nasal cavity, the keratinizing 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 [2]. 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 mucosa lines the horizontal part of the roof of the nasal cavity. The olfactory epithelium is predominantly made of columnar non-ciliated sustentacular cells, intermingled with scattered bipolar sensory neurons and basal cells; the olfactory serous glands of Bowman are located in the lamina propria.

2.2 Acute and Chronic Rhinosinusitis

2.2.1 Acute Rhinosinusitis

Definition Rhinosinusitis is an inflammatory condition of the nasal and paranasal sinus mucosa. Acute rhinosinusitis (ARS) is usually infectious and can be clinically characterized by purulent (not clear) nasal drainage (anterior, posterior, or both) lasting up to 4 weeks, accompanied by nasal obstruction, facial pain-pressure-fullness, or both [3]. In the
immunocompromised patient, the etiology is predominantly viral or bacterial and less often fungal, whereas in immunocompromised patients, acute fungal sinusitis may occur.

**Synonyms** Acute sinusitis and acute rhinitis

**Epidemiology** The true incidence and prevalence of ARS are unknown, because a significant number of cases do not come usually to medical attention. However, the prevalence of rhinosinusitis in the general population is considered to be high, and it is estimated that more than 24 million cases of acute bacterial rhinosinusitis occur annually in the United States [4]. ARS is more common in children than adults. The prevalence of this disease is increased in women. It is generally thought that the process starts in the nasal mucosa and spreads through the ethmoidal prechambers to the frontal and maxillary sinuses.

**Etiology and pathogenesis** Infectious rhinitis is typically viral and is often referred to as “common cold.” It is more common in children than in adults, and the most frequently identified agents are rhinovirus, myxovirus, coronavirus, and adenovirus [3]. Swelling of the mucosa may cause obstruction of a sinus ostium, with subsequent secondary bacterial infection (acute bacterial sinusitis). The most commonly involved agents are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [5, 6]. Allergic rhinitis (hay fever) is part of an inherited syndrome which also may manifest as atopic eczema and asthma. In allergic rhinitis, airborne particles, such as grass pollens, molds, 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 rhinorrhea and nasal obstruction.

A further type of rhinitis is the non-allergic form (non-allergic rhinitis, NAR), which is defined by exclusion as a chronic nasal inflammation which is not caused by systemic IgE-dependent mechanisms [7]. Nasal cytology has allowed the distinction of different NAR types on the basis of the inflammatory infiltrate, which include the non-allergic rhinitis with eosinophils (NARES), the non-allergic rhinitis with neutrophils (NARNE), the non-allergic rhinitis with mast cells (NARMA), and the non-allergic rhinitis with eosinophils and mast cells (NARESMA). Their recognition is important in order to choose the appropriate treatment.

**Macrosopy** The mucosa is thickened and edematous, and there is a prominent exudate, which is purulent in bacterial forms. Necrotic tissue is obtained from debridement procedures in case of acute fungal sinusitis.

**Microscopy** In ARS, histopathologic examination is rarely requested. The sinonasal mucosa demonstrates extensive inflammation, with neutrophil-rich infiltrate. In some cases, hemorrhage and necrosis may also be noted. In acute fungal sinusitis, fungal hyphae can be recognized with appropriate staining methods. The fungus has a tendency to invade blood vessels causing thrombosis and may spread through the perineural spaces [8]. The affected tissues exhibit coagulative necrosis and hemorrhage, while the inflammatory reaction is scant [9]. In allergic rhinitis, the nasal mucosa shows numerous eosinophils, abundant plasma cells, and in some cases 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.

**Differential diagnosis** Clinical data are usually sufficient to separate ARS from other inflammatory conditions. Histochemical stainings for fungi are helpful to recognize acute fungal sinusitis.

**Treatment and prognosis** The treatment of ARS is medical and depends upon the viral or bacterial etiology. Acute bacterial rhinosinusitis usually resolves with antibiotic therapy. Complications are rare and include contiguous infectious involvement of the orbit or central nervous system and can be potentially life-threatening. They include epidural abscesses, subdural empyema, and cerebral abscesses. The incidence of these complications seems to peak in early adolescence. Acute fungal sinusitis is lethal in most cases.

### 2.2.2 Chronic Rhinosinusitis

**Definition** Chronic rhinosinusitis (CRS) comprises a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks' duration [10].

**Synonyms** Chronic sinusitis and chronic rhinitis

**Epidemiology** CRS is a common disease, but the true incidence is difficult to ascertain, mainly due to the lack of uniformly accepted criteria for the diagnosis. However, it is estimated that in the United States, the prevalence of CRS is 14 % of the global population [11, 12].

Children are more prone to suffer of CRS than adults [12]. The prevalence of the disease is higher in women than in men [13].

Incidence of atrophic rhinitis has markedly decreased in the last century, and nowadays most cases are secondary to trauma, surgery, granulomatous diseases, infection, and radiation exposure [14].
Pathogenesis  Local predisposing factors include sinus ostia blockage, repeated episodes of common cold or acute sinusitis determining obstruction of sinus ostia, reduction of ciliary activity (immotile cilia syndrome), and cystic fibrosis. Multiple factors may be involved in the pathogenesis of atrophic rhinitis, including chronic bacterial infections and nutritional deficiencies.

Some patients with predisposing conditions, such as allergy, asthma, transplant, or AIDS, develop CRS more often [12]. Sinonasal infections are frequently observed in HIV patients; they are often asymptomatic and tend to be recurrent or refractory [15]. They are due to various pathogens including cytomegalovirus [16], *Staphylococcus aureus*, fungi (*Aspergillus* sp.) [17], and parasites (*Microsporidia, Cryptosporidium*) [18].

Variants of CRS  Atrophic rhinitis is a chronic inflammation of the nasal mucosa of unknown etiology characterized by progressive nasal mucosal atrophy and by a thick, dense secretion, with fetid smelling and crusting [14]. Hypertrophic rhinitis is characterized by thickening of the sinonasal mucosa resulting from chronic inflammatory diseases [10, 19]. Frequently these patients have undergone several sinus operations, each time with limited success and subsequent recurrence. Recurrent nasal polyposis is often associated.

Macrosopic  The mucosa is thickened, edematous, and gray white in color. In atrophic rhinitis, the mucosa becomes atrophic.

Microscopic  The mucosal changes observed are variable and include basement membrane thickening, goblet cell hyperplasia, mucous gland hyperplasia, edema of varying extent, inflammation (mostly lymphocytes, plasma cells, and eosinophils), and polypoid change of the mucosa. The histopathological patterns do not always correlate with the clinical features although in atrophic rhinitis the nonspecific chronic inflammatory infiltrate goes with squamous metaplasia of the surface epithelium and of glandular excretory ducts and atrophy of seromucous glands [20, 21].

Differential diagnosis  The differential diagnosis is with chronic inflammatory processes, including granulomatous infections, granulomatosis with polyangitis (Wegener’s), Churg-Strauss disease, and other noninfectious midline granulomas.

Treatment and prognosis  Medical treatment (decongestants, antihistamines, topical steroids) is recommended for most forms of CRS. Surgery is indicated in case of persistence of symptoms despite medical therapy, for correction of anatomic deformities believed to be contributing to persistence of disease and for debulking of advanced nasal polyps. CRS may relapse and eventually complicate in sinonasal inflammatory polyposis and mucocele formation.

2.3  Sinonasal Polyps

Definition  Sinonasal polyps are nonneoplastic pedunculated swellings of the sinonasal mucosa. When multiple, they are referred as polyposis. The majority of them are inflammatory allergic. Other polyps are of infective, chemical, or familial etiology. The histological appearances of nasal polyps do not always correlate well with their etiology.

2.3.1  Inflammatory Allergic Polyps

Definition  Inflammatory allergic polyps (IAPs) are those inflammatory swellings of the sinonasal mucosa of allergic origin.

Synonym  Inflammatory polyp

Epidemiology  IAPs develop in patients of all ages, being most commonly seen over 20 years of age. They arise most frequently from the upper part of the lateral nasal wall and from the ethmoidal region. Nasal cavities and paranasal sinuses may be simultaneously involved, either unilateral or bilateral.

Etiology and pathogenesis  IAPs are due to allergens that trigger the path of the hypersensitivity reaction type I (see Sect. 2.2.1).

Macroscopic  IAPs are grapelike formations of soft consistency and glassy appearance, measuring from a few millimeters to several centimeters.

Microscopic  IAPs are made up largely of myxoid edematous tissue with pseudocysts containing eosinophilic proteinaceous fluid and infiltrates of inflammatory cells usually exhibiting heavy infiltration by eosinophils (Figs. 2.1 and 2.2), being accompanied by variable number of plasma cells and some mast cells [22]. They are covered by respiratory epithelium with goblet cell hyperplasia, squamous metaplasia, and thickening of the basement membrane. Seromucous glands with mucin-containing cysts may also occur (Fig. 2.3). Epithelial dysplasia may be present in rare cases. Granulomas may be seen 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 [23]. These atypical cells occur individually and are more frequently found close to blood vessels.
(Fig. 2.4) or near the epithelial surface. Such stromal atypia is a reactive phenomenon that should not be mistaken for sarcoma.

**Treatment and prognosis** Complete excision is curative, although recurrences may occur if exposure to allergens persists.

### 2.3.2 Other Polyps

#### 2.3.2.1 Antrochoanal Polyp

**Definition** Antrochoanal polyps (ACPs) are single polyps that arise in the maxillary sinus, also known as antrum, and extend into the middle meatus projecting posteriorly through the ipsilateral choana [24]. Those polyps that arise in the maxillary antrum and extend into the middle meatus projecting anteriorly are known as antronal polyps. Killian polyp is a synonym of ACP commonly used by rhinologists.

**Epidemiology** ACPs account for about 5% of all sinonasal polyps. Patients with ACP are younger than those with IAPs.

**Macroscopy** ACP is characterized by a long and thin stalk which originates in the maxillary mucosa.

**Microscopy** Typically ACPs are devoid of the marked eosinophilic infiltrate of IAPs and have sparser content in mucous glands than the latter. ACPs usually have a prominent fibrous stroma which surrounds thick-walled blood vessels (Fig. 2.5) [25]. In addition, scattered, enlarged, stromal cells with hyperchromatic nuclei are not an
uncommon finding in ACPs that should not be confused with sarcoma [26].

**Differential diagnosis** ACP must be differentiated from juvenile angiofibroma, as well as from low-grade sarcoma.

**Treatment and prognosis** Complete resection, stalk included, is curative.

### 2.3.2.2 Polyposis in Cystic Fibrosis

**Definition** Sinonasal polyps occurring in the context of cystic fibrosis (CF).

**Synonym** Polyposis in mucoviscidosis

**Pathogenesis** CF is an autosomal disorder affecting children with the presence of thick mucus, which obstructs, among other ducts, the lumina of the airways and impairs mucociliary function. CF is due to mutations of the *CFTR* gene located at 7q31.2 [27].

**Microscopy** Nasal polyps in mucoviscidosis show cystic glands filled with inspissated mucoid material and thickening of the basement membranes that surround the glands [28, 29].

### 2.3.2.3 Polyposis in Immotile Cilia Syndrome and Kartagener Syndrome

Immotile 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 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 in immotile cilia syndrome [30]. Mutations have been detected in the following genes: *DNAI1*(7p21), *DNAH5* (5p14-5p15), and *DNAH11*(7p21) [31].

### 2.3.2.4 Angiomatoid Sinonasal Polyp

**Definition** Angiomatoid sinonasal polyps (ASNPs) are characterized by the conspicuous proliferation of small blood vessels, mostly capillaries, occurring within the myxoid background of conventional sinonasal polyps [32].

**Epidemiology and etiology** ASNP is a rare complication of IAPs and ACPs that may be due to trauma or be iatrogenic.

**Microscopy** The angiomatoid changes seen in ASNPs are characterized by the proliferation of numerous small blood vessels within a myxoid background. Thrombotic phenomena with heavy fibrin deposition are seen in nearly 50% of cases. Necrosis is always present if thoroughly searched. Cellular atypia can be prominent but mitosis are rare and atypical mitoses are absent [32].

**Differential diagnosis** ASNPs must be differentiated from angiosarcoma. Although cellular atypia can be prominent in ASNPs, malignancy is ruled out by the scarce number of mitotic figures and the absence of atypical mitoses [33].

**Treatment and prognosis** Complete excision is curative.

### 2.4 Sinonasal Heterotopias and Hamartomas

#### 2.4.1 Heterotopic Neuroglial Tissue and Encephalocele

**2.4.1.1 Heterotopic Neuroglial Tissue**

**Definition** Heterotopic neuroglial tissue (HNGT) is a mass of displaced mature neuroglial tissue presenting intranasally, in the adjacent nasal subcutaneous tissue or in both.

**Synonyms** Glial heterotopia and nasal glioma, although the latter is a misnomer

**Epidemiology** HNGT mostly occurs in young children.

**Etiology and pathogenesis** Usually, HNGT is the result of a congenital abnormality related to a variant of meningoencephalocele in which connection with the intracranial central nervous system is lost [34, 35]. The lesion mainly arises at the base of the nose or in the upper part of the nasal cavity.
**Macroscopy**  HNGT may be polypoid and rarely measures more than 2 cm.

**Microscopy**  Histologically, HNGT is mostly composed of a mixture of astrocytes, glial fibers, and fibrous connective tissue. Multinucleated glial cells are not infrequently found (Fig. 2.6). Some glial cells can have large nuclei resembling nerve cells. A few true nerve cells or even ependymal elements can rarely be identified. Mitoses are not found. Bona fide gliomas may occur in association with HNGT [36].

**Immunohistochemistry**  Staining for S-100 protein and glial fibrillary acidic protein is positive, the latter being a helpful diagnostic adjunct.

**Treatment and prognosis**  Complete surgical excision is curative. Recurrence may follow incomplete resection.

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### 2.4.1.2 Encephalocele

**Definition**  Nasal encephalocele (EC) is the result of the herniation of brain tissue and its leptomeningeal covering through an osseous defect of the nasal roof.

**Synonym**  Meningoencephalocele

**Epidemiology**  EC mainly occurs in older children and also in adults.

**Etiology and pathogenesis**  An osseous defect at the base of the skull, usually due to trauma, surgery, or infections, facilitates the herniation of the brain.

**Microscopy**  EC displays a mixture of neural, glial, and leptomeningeal elements.

**Differential diagnosis**  In contrast to heterotopias, encephaloceles are communicated with the central nervous system, and tissues are fairly organized although they can show dysplastic changes [37]. In addition EC has to be distinguished from glioma and teratoma.

**Treatment and prognosis**  Complete resection of EC with repair of the osseous defect at the base of the skull is mandatory to achieve cure.

### 2.4.2 Hamartomas

**Definition**  Benign polypoid overgrowths in which well-developed epithelial and mesenchymal sinonasal tissues are present with variable participation [38]. Three types are recognized: respiratory epithelial adenomatoid hamartoma, chondro-osseous and respiratory epithelial hamartoma, and nasal chondromesenchymal hamartoma.

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#### 2.4.2.1 Respiratory Epithelial Adenomatoid Hamartoma

**Definition**  Respiratory epithelial adenomatoid hamartoma (REAH) is a benign polypoid lesion with well-developed branching glands covered with ciliated respiratory epithelium [38].

**Epidemiology**  REAH occurs in adults and is equally frequent in men and women [39].

**Etiology and pathogenesis**  The cause is unknown. REAH may be the result from an exuberant hyperplastic reaction within an inflammatory context, as most of cases develop in association to nasal polyposis [39].

**Molecular genetics**  The molecular profile of REAH shows tumor suppressor gene alterations with a mean fractional allelic loss of 31 %, an unusually high percentage for a non-neoplastic entity, suggesting the possibility that may be a benign neoplasm rather than a hamartoma [40].

**Macroscopy**  Polypoid formations of soft consistency measuring up to several centimeters.

**Microscopy**  The seromucous epithelium of the deep mucosal glands in REAHs is characteristically replaced by ciliated respiratory epithelium admixed with goblet cells accompanied by thick bands of fibrous stroma in the underlying supportive tissue (Figs. 2.7 and 2.8). When the deep glandular component
is maintained and the overgrowth mainly consists of disorderly placed seromucinous glands, lacking myoepithelial cells, the term “seromucinous glandular hamartoma” (SMGH) is used [41, 42] (Figs. 2.9 and 2.10).

**Differential diagnosis** REAH and SMGH must be differentiated from sinonasal polyps, inverted papilloma, and the various types of low-grade adenocarcinomas [43]. The latter may show CK20 or CDX2 immunohistochemical expression, not reported in hamartomatous lesions [44].

**Treatment and prognosis** Conservative complete excision is curative [45].

### 2.4.2.2 Chondro-osseous and Respiratory Epithelial Hamartoma

**Definition** Chondro-osseous and respiratory epithelial hamartoma (COREH) combines the features of REAH with juxtaposed cartilaginous and osseous structures.

**Macroscopy** COREH is similar in shape to REAH but has harder consistency and abundant cystic formations on the cut section (Fig. 2.11).

**Microscopy** Immature to mature benign chondral and osseous trabeculae appear juxtaposed with gland-like formations
covered with respiratory epithelium and supportive fibrous stroma (Fig. 2.12) [46].

Differential diagnosis COREH must be mainly distinguished from nasal chondromesenchymal hamartoma. The latter mostly occurs in children and the former in adults.

Treatment and prognosis As in REAH, conservative complete resection is curative.

2.4.2.3 Nasal Chondromesenchymal Hamartoma Definition Nasal chondromesenchymal hamartoma (NCMH) is a benign pseudotumoral overgrowth composed of an admixture of chondroid, stromal, and cystic spaces.

Epidemiology and pathogenesis NCMHs are more frequent in nasal cavities, they can also arise from the nasopharynx and paranasal sinuses [41]. The cause is unknown. The occurrence of NCMH as initial lesion in children with pleuropulmonary blastoma predisposition syndrome has been reported [49]. In this disorder, NCMH arises secondary to germline and somatic mutations of the gene DICER1.

Macroscopy NCMH can reach up to 8 cm in size [48].

Microscopy NCMH consists of irregular nodules of mature hyaline cartilage in lobular arrangement. The chondroid nodules are surrounded by stroma that may be loose and myxoid or dense and collagenous. Blood-filled cystic spaces with features similar to aneurysmal bone cyst, as well as microcysts, within the myxoid areas can be seen. Ossicles, trabeculae of immature bone, osteoclast-like giant cells, and foci of mature adipose tissue can be found occasionally. The stromal spindle cells usually are positive for smooth muscle actin and the chondroid cells for S-100 protein.

Differential diagnosis NCMH needs to be distinguished from COREH, chondrosarcoma, mesenchymal chondrosarcoma, and chondroblastoma, entities that are exceedingly rare in newborns. The ectomesenchymal chondromyxoid tumor, although sharing certain similarities with NCMH, only occurs in the oral cavity.

Treatment and prognosis Combined intranasal and neurosurgical approach may be required to achieve complete resection, which is curative [48].

2.5 Pseudotumors

2.5.1 Mucocele

Definition Mucocele is a cyst filled with mucous that develops within a sinus cavity as the result of occlusion of the ostium.

Epidemiology The most common sites of occurrence are the frontal and the sphenoidal sinuses.

Etiology and pathogenesis Most commonly is due to infection but also may result from trauma or be congenital [50]. Retained secretions cause expansion of the sinus and bone erosion.

Microscopy The cyst is lined by respiratory epithelium that shows prominent goblet cell hyperplasia [51, 52]. Expansion of the cyst may cause atrophy and metaplasia of the epithelium.
Treatment and prognosis Surgical evacuation of the involved sinus by removal of the occlusion achieves excellent results.

2.5.2 Necrotizing Sialometaplasia

Definition Necrotizing sialometaplasia (NSM) is a reactive change of seromucous glands that undergo squamous metaplasia.

Etiology and pathogenesis Etiology relates to an ischemic event. Trauma has been claimed also as a cause of these lesions.

Clinical aspects It presents as a localized swelling that becomes ulcerated.

Microscopy Glandular lobular architecture is preserved, with squamous metaplasia of ducts and acini and glandular infarction. Mucin spillage elicits inflammation. The overlying epithelium can show pseudoepitheliomatous hyperplasia.

Differential diagnosis The most important entities to be considered are squamous cell carcinoma (SCC) and mucoepidermoid carcinoma. Proliferation in NSM is usually low, a feature that can be helpful in the distinction.

Treatment and prognosis Healing occurs spontaneously; therefore, surgical treatment is not necessary [53].

2.5.3 Organizing Hematoma

Definition Sinonasal organizing hematoma (OH) is a mass of hemorrhage in the nose and paranasal sinuses.

Synonyms “Cholesterol granuloma” and “rhinitis caseosa”

Etiology and pathogenesis OH is in most cases the result of occult submucosal hemorrhage in the maxillary sinus due to external trauma or tooth extraction. Resolution of the hematoma produces the formation of cholesterol granulomas [54].

Macroscopy A sessile mass is seen, consisting of dark-red hemorrhagic areas admixed with pale “cheesy” zones composed of cholesterol.

Microscopy In OH, large areas of degenerated blood and deposits of fibrin predominate, which are being organized by granulation tissue. Resolution of the hematoma produces the formation of cholesterol granulomas and fibrosis, simulating a foreign body reaction. Often, there are areas of irregular blood vessels, occasionally lined by bizarre endothelial cells, which may be mistaken for a malignant vascular tumor [55].

Differential diagnosis OH must be mainly differentiated from angiosarcoma.

Treatment and prognosis Surgical removal of the mass is curative.

2.5.4 Amyloidosis

Epidemiology Isolated amyloid deposition in the sinonasal mucosa is a rare event, with about 20 cases reported in the English literature [56, 57].

Macroscopy Grossly, the lesion appears as a friable to hard tumorlike mass, with frequent hemorrhage.

Microscopy Histologically, there is a deposition of intensely eosinophilic material in the stroma, around blood vessels and around ducts of seromucous glands, which is often associated with diffuse chronic inflammation and foreign body granulomatous reaction. Amyloid stains orange with Congo red and is apple-green birefringent at polarized light examination. Immunohistochemistry may help to identify the type of amyloid deposition. In the head and neck, most cases are of the primary (AL) type; therefore, they show immunoreactivity with AL (kappa or lambda light chain amyloid) [58].

Differential diagnosis OH must be mainly differentiated from angiosarcoma.

Treatment and prognosis Surgical removal has a palliative purpose.

2.5.5 Myospherulosis

Definition Myospherulosis is characterized by the presence of cyst-like spaces lined by flattened histiocytes and containing clusters of brownish spherules resembling fungi [59–61].

Epidemiology Myospherulosis is a rare entity, with less than 200 cases reported [62].

Etiology and pathogenesis The lesion is usually found in patients who have had previous operations [63]. It is now recognized that the spherules are extravasated red cells that have been altered by interaction with traumatized fat or petrolatum-based ointments and gauzes used in surgical procedures.

Microscopy The spherules lie loosely or within sacs formed by thin refractile membranes. The brownish spherules do not
stain with PAS or Gomori methenamine silver, and their morphology does not correspond with any known fungus [64]. They are found within fibrous granulation tissue which may show a foreign body reaction.

**Treatment and prognosis** Surgical removal produces excellent results.

### 2.5.6 Eosinophilic Angiocentric Fibrosis

**Definition** Eosinophilic angiocentric fibrosis (EAF) is a disorder that compromises the airways due to progressive obstruction.

**Etiology and pathogenesis** Recent findings support that EAF is part of the spectrum of IgG4-related systemic diseases [65, 66].

**Epidemiology** EAF is a rare, chronic, benign, condition of the upper respiratory tract occurring predominantly in adult women [67, 68].

**Microscopy** Initially, the histologic picture is characterized by non-necrotizing eosinophilic vasculitis involving capillaries and venules of the sinonasal mucosa, accompanied by an inflammatory infiltrate with lymphocytes, plasma cells, histiocytes, and occasional neutrophils (Fig. 2.13). In late lesions, there is a characteristic obliterative perivascular onionskin fibrosis, while the inflammatory infiltrate is less dense (Fig. 2.14) [67].

The differential diagnosis includes reactive processes of the sinonasal mucosa, like granulomatosis with polyangiitis (Wegener’s), Churg-Strauss disease, Kimura disease, angio-lymphoid hyperplasia with eosinophilia, and IgG4-associated disease.

**Treatment and prognosis** Surgery offers palliation of the nasal obstruction.

### 2.5.7 Surgical Ciliated Cyst of the Maxilla

**Definition** Surgical ciliated cyst of the maxilla is a locally aggressive lesion that develops mainly as a complication of surgery in the maxillary sinus region [69, 70].

**Synonyms** Postoperative maxillary cyst and paranasal cyst

**Epidemiology and pathogenesis** The incidence is variable. It represents 19.5% of all oromaxillary cystic lesions in the Japanese population [69], while it is rare in Europe and the United States. It occurs in adult subjects, with a mean age of 52 years [71]. There is no significant gender predilection [70, 71]. This cyst usually arises in the lateral wall of the maxilla and expands toward the canine fossa or toward the nasal wall or sphenopalatine wall of the sinus. Some lesions may be more aggressive and occupy the orbit floor or ethmoidal air cells (Fig. 2.15). There are also reports of mandibular localization. The lesion is likely to be caused by sinus or nasal mucosa entrapment in the bone healing process after an osteotomy in these sites.

**Macroscopy** Surgical ciliated cyst is usually unilocular, but multilocular lesions have also been observed. The wall
shows variable thickness, and the content is brown mucinous, more rarely serous. Purulent fluid and cholesterol crystals are frequently seen [70].

**Microscopy** The wall of the cyst characteristically displays a fibrous connective tissue band, often with mild-to-moderate inflammatory infiltrate, which appears entrapped between the osseous wall and the overlying mucosa (Fig. 2.16). The mucosa is lined by an epithelium, which is pseudostratified ciliated in two-thirds of the cases, transitional in 28% and squamous in 6%. Goblet cells are also present, and their number increases with local infiltration of inflammatory cells into the cyst wall [71]. Epithelial dysplasia has been rarely observed [70].

**Differential diagnosis** Surgical ciliated cyst should be differentiated from mucocele of the maxillary sinus, which presents as a cyst containing mucoid or gelatinous material, lined by pseudostratified ciliated epithelium, sometimes with areas of squamous metaplasia. However, the main difference with surgical ciliated cyst is that paranasal sinus mucocele is not found in intraosseous location. Odontogenic cysts, including radicular cysts and keratocyst, may also occasionally present areas of ciliated epithelium. The clinical history of previous surgery of the maxillary sinus (Caldwell-Luc procedure) and the radiological aspect of the lesion are helpful in the distinction [72].

**Treatment and prognosis** Treatment consists of surgical removal of the lesion. Removal of the lesion is curative.

**2.6 Fungal Diseases**

**2.6.1 Allergic Fungal Rhinosinusitis**

**Definition** The allergic form of fungal rhinosinusitis (FRS) is a non-invasive form of fungal infection, due to a localized hypersensitivity response to fungal growth that arises in areas of compromised mucus drainage.

**Synonym** Eosinophilic fungal sinusitis
**Epidemiology**  Allergic FRS is the most common of all fungal sinusitis and accounts for between 5 and 10% of all chronic rhinosinusitis cases [73]. It most commonly affects adolescents and young adults (mean age at diagnosis 21.9 years) [74]. There is no significant gender predilection. The maxillary, ethmoid, and sphenoid sinuses are most commonly involved. Unilateral involvement may occur in some cases [74]. It is associated with nasal polyps, atopy, asthma, and elevated serum IgE [75].

**Etiology**  In the first description of this disease, *Aspergillus* sp. was recognized as the primary causative fungus [76], but subsequent reports have evidenced that fungi of the dematiaceous family (*Alternaria* sp., *Bipolaris* sp., *Curvularia* sp., and others) are implicated in the majority of the cases [77].

**Macroscopy**  At the time of surgery, allergic fungal mucin is recognized as thick and highly viscous in consistency, varying in color from light tan to brown, black, or dark green.

**Microscopy**  The histological features necessary for the diagnosis of allergic FRS are detected in the mucin, rather than in paranasal sinus mucosa, which shows the changes of a non-specific inflammatory condition, without involvement by fungi. The hallmark of the disease is the production of allergic mucin in which mucous material alternates with cell debris conferring a wavy appearance (Fig. 2.17). With hematoxylin and eosin stain, the mucin has a basophilic background and contains a mixed inflammatory cell infiltrate with a predominance of eosinophils, necrotic cell debris, and Charcot-Leyden crystals (Fig. 2.18). Fungal hyphae are rare, scattered, and fragmented and can be identified within the mucin with histochemical stainings (Fig. 2.19), including Grocott and Gomori methenamine silver [76, 78]. When fungal hyphae are not identified, the term sinonasal allergic mucinosis is applied.

**Differential diagnosis**  Allergic FRS must be differentiated from other sinonasal fungal diseases, particularly from invasive forms, including indolent, granulomatous, and fulminant variants [9]. These are rare diseases in which fungi are found in the mucosa, soft tissues, and bone [76]. Chronic non-invasive fungal sinusitis, also known as fungus balls or mycetomas, is recognized as self-limited collections of matted fungal hyphae confined most commonly to the maxillary sinus.

**Treatment and prognosis**  To prevent recurrences, a combination of conservative surgery and adjunctive medical

| Table 2.1 Fungal diseases of sinonasal tract |
|---------------------------------------------|
| Non-invasive rhinosinusitis | Tissue-invasive rhinosinusitis |
| Allergic fungal sinusitis | Invasive indolent |
| Fungus ball | Invasive fulminant |

Fig. 2.17  Allergic mucinosis: basophilic pools of mucin alternate with dense aggregates of eosinophilic leukocytes conferring a wavy appearance

Fig. 2.18  Allergic mucinosis: a Charcot-Leyden crystal between lakes of mucin and aggregates of eosinophilic leukocytes

Fig. 2.19  Allergic fungal sinusitis, scarce fungal hyphae in a lake of mucin. Gomori methenamine silver
treatments, including systemic and/or topical corticosteroids, and immunotherapy to pertinent fungal and nonfungal antigens is recommended [75, 79].

2.6.2 Non-invasive Fungal Rhinosinusitis

**Definition** Non-invasive FRS is a mycotic infection characterized by the presence of a fungus ball in the sinus lumen, without involving the adjacent tissues.

**Synonyms** Mycetoma, fungus ball, and extramucosal fungal sinusitis

**Epidemiology** The maxillary sinus is the most commonly involved. Ethmoid, frontal, and sphenoid sinuses are affected less often.

**Etiology and pathogenesis** Non-invasive FRS occurs in immunocompetent patients, being mainly caused by *Aspergillus* sp. Other fungi are less common.

**Macroscopy** The consistency of the fungus ball may vary from soft to hard with focal central calcification.

**Microscopy** As a non-invasive disease, the fungal mass is present in the lumen of the sinus. Usually, the neighboring mucosa shows mild chronic inflammation. In sections stained with PAS-diastase or Gomori methenamine silver, the *Aspergillus* sp. hyphae appear as dichotomously, acute-angle branching septate hyphae 6–8 μm wide (Fig. 2.20).

**Differential diagnosis** Allergic FRS and invasive forms of fungal sinusitis must be ruled out.

**Treatment and prognosis** Evacuation of the sinus with removal of the fungus ball by endoscopic surgery is the recommended option. Antifungal medication is not required.

2.6.3 Invasive Fungal Rhinosinusitis

The spectrum of invasive FRS covers the chronic indolent invasive and the acute fulminant forms [9, 75]. The first form is found in immunologically competent patients and the latter is restricted to immunocompromized patients.

2.6.3.1 Chronic Invasive Fungal Rhinosinusitis

**Definition** Chronic invasive FRS is an uncommon form of sinusitis characterized by a protracted clinical course despite the finding of fungal tissular invasion. Chronic indolent invasive fungal sinusitis is a synonymous.

**Epidemiology** Two forms of chronic invasive FRS are recognized: the nonspecific chronic invasive fungal sinusitis and the granulomatous chronic invasive fungal sinusitis [80].

**Etiology and pathogenesis** Both of these conditions are thought to be due to *Aspergillus* sp. and both occur in immunologically competent patients.

**Microscopy** Fungi are found in the mucosa, soft tissues, and bone. The presence of a granulomatous reaction, the recognition of which is strictly a function of histopathology, is currently the sole means of identifying this category [75]. At present, there is no histopathologic hallmark diagnostic of nonspecific chronic invasive FRS, which may be better labeled as “nongranulomatous chronic invasive” FRS.

**Treatment and prognosis** Surgical debridement and drainage are required. Systemic antifungal drugs may not be necessary to achieve favorable response to treatment.

2.6.3.2 Fulminant Invasive Fungal Rhinosinusitis

**Definition** Invasive fulminant FRS is an acute, rapidly progressive, and life-threatening fungal infection characterized by destructive tissue invasion with or without obvious vascular invasion.

**Epidemiology** Invasive fulminant FRS is most commonly seen in adult immunocompromised patients.

**Etiology and pathogenesis** Invasive fulminant FRS has been traditionally associated with *Mucor* sp. and poorly controlled diabetics [81], but currently, invasive fulminant FRS also encompasses *Aspergillus* sp., as well as dematiaceous and non-dematiaceous fungi, with a strong association with immunodeficiencies [75].
Microscopy Invasive fulminant FRS causes destructive inflammation of the sinonasal tissues featured by a combination of necrotic debris and tissue invasion with or without obvious vascular invasion [75, 82]. Fungi are found in the mucosa, soft tissues, and bone [76]. The fungus invasion of the blood vessels causes thrombosis, and the surrounding affected tissues may exhibit coagulative necrosis and hemorrhage, while the inflammatory reaction is scant. Although the architecture of the surrounding tissues may fade away, the fungi can often be recognized (Fig. 2.21). In tissue sections stained with PAS-diastase or Gomori methanamine silver, the Mucor sp. fungi are seen as 10- to 20-μm-wide nonseptate hyphae, usually branching at right angles, whereas Aspergillus sp. hyphae appear as dichotomously, acute-angle branching septate hyphae 6–8 μm wide.

Differential diagnosis Invasive fulminant FRS must be differentiated from other types of fungal sinusitis, as well as from other midfacial destructive and granulomatous lesions.

Treatment and prognosis The therapy for patients with acute fungal sinusitis is multimodal and involves surgery and antibiotic therapy. Aggressive surgical debridement and drainage and systemic antifungal drugs are mandatory. A quick histological recognition of the fungi is of paramount importance in the proper management of invasive fulminant FRS. A frozen section may be required from the pathologist, as fungal cultures are often negative and an early diagnosis and treatment improves survival rates and lowers morbidity [8].

2.6.4 Rhinosporidiosis

Definition Rhinosporidiosis (RSP) is a special form of chronic invasive granulomatous fungal disease that follows a protracted course, growing in the form of polyps involving the upper respiratory tract, principally the nasal cavity [83, 84].

Epidemiology Most cases of RSP occur in India and Sri Lanka and less frequently in Brazil. Although very rarely, RSP may be seen in any country.

Etiology and pathogenesis RSP is caused by the endosporulating fungus Rhinosporidium seeberi. It affects immunocompetent patients through endospores contaminating water or soil.

Macroscopy RSP lesions may look alike allergic sinonasal polyps.

Microscopy In RSP the mucosal and submucosal involvement is characterized 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. Sporangia also stain with PAS-diastase and Gomori methanamine silver.

Differential diagnosis Sinonasal polyps and papillomas, as well as coccidiomycosis

Treatment and prognosis Surgical removal of the lesions. Recurrence rate is low.

2.7 Midfacial Destructive Granulomatous Lesions

2.7.1 Granulomatosis with Polyangiitis

Definition Granulomatosis with polyangiitis (GPA) is an immunologically mediated inflammatory disease characterized 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.

Synonym Wegener’s granulomatosis

Epidemiology GPA lesions in the upper respiratory tract are ulcerative and destructive and occur mainly in the nasal cavity and paranasal sinuses. At the time of initial presentation, the full clinical picture of the disease is rarely seen.

Clinical aspects A high percentage of patients develop elevated c-ANCA as well as elevated proteinase 3 (PR3).
Microscopy  The hallmarks of GPA 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 (Figs. 2.22 and 2.23) [85–90].

Differential diagnosis  The classic histological features of GPA are not present in many biopsy specimens. Repeat biopsies and clinical correlations are often essential for early diagnosis. In the early stages, when GPA is restricted to the upper respiratory tract and ear, the diagnosis can be quite difficult [90]. Stains for acid-fast bacilli and fungi are negative. GPA must be differentiated from allergic granulomatosis and vasculitis (AGV) also known as Churg-Strauss disease, in which, besides vasculitis and poorly formed granulomas, eosinophils predominate with formation of eosinophilic microabscesses [89]. In AGV, c-ANCA may be occasionally elevated but PR3 is absent. NK-/T-cell lymphoma and diffuse large B-cell lymphoma are other differential diagnoses. Increased IgG4-positive cells can be seen in sinonasal, orbital, and periorbital biopsies of GPA that could induce a wrong diagnosis of IgG4-related disease [66].

Treatment and prognosis  Concomitant administration of cyclophosphamide and prednisone is recommended [90].

2.7.2  Leprosy

Definition  Leprosy is a chronic infection caused by *Mycobacterium leprae* that depending on the immunoreactivity of the patients presents three clinical forms: lepromatous, tuberculoid, and indeterminate.

Epidemiology and pathogenesis  *Mycobacterium leprae* affects principally the cooler parts of the body as the upper respiratory tract and especially the sinonasal region [91, 92].

Microscopy  Lepromatous leprosy is the most frequent form of this disease involving the nasal cavity [93]. It is characterized by nodular masses of foamy macrophages (Virchow lepra cells) in which large numbers of acid-fast bacilli (*Mycobacterium leprae*) are demonstrable by the Fite-Faraco stain, a modified Ziehl-Neelsen method. Tuberculoid leprosy is characterized by non-caseating granulomas and the indeterminate variant by a nonspecific chronic inflammatory reaction; acid-fast bacilli are seldom demonstrable in these types.

Treatment  Combination of rifampicin, dapsone, and clofazimine

2.7.3  Tuberculosis

Definition  Tuberculosis (TBC) is a chronic granulomatous infection caused by *Mycobacterium tuberculosis*.

Epidemiology  Tuberculosis (TBC) of the head and neck occurs infrequently, and involvement of the nose is rare, representing in most cases a secondary event to pulmonary involvement [94].

Macroscopy  In most cases, there is a polyp of the nasal septum or an ulcerated granular lesion.

Microscopy  TBC is characterized by caseating and confluent granulomas with surrounding epithelioid cells palisading
and Langhans-type giant cells. Lack of caseation is uncommon. Histologically, acid-fast bacilli may be occasionally identified by the Ziehl-Neelsen stain. The definitive diagnosis is made by isolating *Mycobacterium tuberculosis* by culture and/or PCR from tissue removed during biopsy.

**Differential diagnosis** It includes all other granulomatous diseases, mainly those with caseating type of necrosis. The presence of intracranial extension may lead to a clinical diagnosis of malignancy [95].

**Treatment and prognosis** Administration of tuberculostatic drugs is usually curative.

### 2.7.4 Sarcoidosis

**Definition** Sarcoidosis is a chronic multisystem, non-caseating granulomatous disorder of unknown etiology. The upper aerodigestive tract is occasionally involved.

**Epidemiology** Besides the lung, hilar and mediastinal lymph nodes, skin, liver, and other systems and organs, several head and neck territories may be affected. The sinonasal mucosa is rarely involved, and most patients have generalized disease [96–99].

**Microscopy** Discrete non-caseating and non-confluent granulomas are a distinguishing feature. Sarcoid granulomas are composed predominantly of epithelioid histiocytes with multinucleated giant cells and a peripheral rim of lymphocytes. Asteroid bodies and Schaumann’s conchoid calcium concretions may be found in the cytoplasm of the giant cells. Stains for acid-fast bacilli and for other infectious agents are negative. Although no microorganisms are found in sarcoid granulomas, cell wall-deficient forms of mycobacteria have been detected by PCR [100].

**Differential diagnosis** Includes other granulomatous disorders, like tuberculosis, leprosy, granulomatosis with polyangiitis, inhalant granulomatous processes, and cholesterol granuloma [85].

**Treatment and prognosis** Corticosteroids are recommended for treatment of clinically active disease. Outcome is usually favorable. Low-dose corticosteroid treatment may be required to maintain remission and prevent fibrosis.

### 2.7.5 Rhinoscleroma

**Definition** Rhinoscleroma (RNS) is a chronic bacterial infection caused by *Klebsiella rhinoscleromatis*.

**Epidemiology** RNS is most prevalent in Russia, Belarus, Poland, and central European countries. Central and upper South American countries are also endemic areas [101].

**Etiology** *Klebsiella rhinoscleromatis* is a capsulated gram-negative bacillus [83, 101].

**Macroscopy** Large nodular tumorlike masses are found in the nasal cavity (Hebra nose). Less often, RNS nodules are found in other parts of the upper respiratory tract.

**Microscopy** RNS nodules contain large macrophages with abundant clear or vacuolated cytoplasm, known as Mikulicz cells (Fig. 2.24). The causative organism may be seen within these cells by the H&E stain; however, they are better identified by the Warthin-Starry staining method or by immunostaining for the *Klebsiella* capsular antigen. In addition, there is fibrosis and heavy infiltration by chronic inflammatory cells, mainly plasma cells showing numerous Russell bodies. The mucosal epithelium may show squamous metaplasia and occasionally prominent pseudoepitheliomatous hyperplasia. Exceptional examples of squamous cell carcinoma have been reported, in association with RNS [83, 101–103].

**Differential diagnosis** RNS must be ruled out from leprosy, syphilis, yaws, TBC, leishmaniasis, rhinosporidiosis, and paracoccidioidomycosis [101]. Another entity to be distinguished from RNS is Rosai-Dorfman disease.

**Treatment and prognosis** Prolonged treatment by tetracycline and ciprofloxacin is recommended. Surgery may be used for debulking the obstruction.
2.7.6 Leishmaniasis

**Definition** Cutaneous leishmaniasis is an infection of the skin by a protozoan of the genus *Leishmania*. It comprises three different entities: localized cutaneous leishmaniasis, also known as “oriental sore” or “tropical sore,” mucocutaneous leishmaniasis, and disseminated anergic cutaneous leishmaniasis [104].

**Epidemiology** Leishmaniasis of the nasal region when seen in Mediterranean and Oriental countries is mostly in the form of “oriental sore” caused by *Leishmania tropica*. In Central and South America, leishmaniasis is mostly seen in the form of mucocutaneous leishmaniasis caused by *Leishmania braziliensis* [105, 106]. Disseminated anergic cutaneous leishmaniasis develops in hosts lacking specific cell-mediated immune responses to the distinct species of *Leishmania*. The parasites are transmitted through the bites of blood-sucking female sand flies of the genus *Phlebotomus* [104].

**Microscopy** The protozoan parasite (amastigote) is seen in the cytoplasm of histiocytes or, extracellularly, measures 1.5–3.0 μm in maximum dimension and has a nucleus and a rod-shaped kinetoplast which 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 disfiguring with marked destruction of the nasal septum in mucocutaneous leishmaniasis. In anergic cutaneous leishmaniasis, the nodules show enormous amounts of histiocytes repleted with leishmania [104].

**Differential diagnosis** Nasal leishmaniasis must be differentiated from other granulomatous diseases such as rhinoscleroma, paracoccidioidomycosis, yaws, leprosy, syphilis, TBC, and histoplasmosis.

**Treatment and prognosis** Antimonial compounds remain the treatment of choice. Prognosis is good in oriental sore, resistant to healing in the mucocutaneous form, and unfavorable in anergic leishmaniasis.

2.7.7 Cocaine Abuse

Cocaine abuse (snorting) may be associated with severe nasal necrotizing inflammation [107]. Endoscopically, there is atrophy of the inferior and middle turbinates and ulceration of the nasal septum. Histologically, areas of necrosis are admixed with acute and chronic inflammation; giant cells embracing birefringent foreign body particles are often present; however, vasculitis is minimal or absent. The lesion may be confused with granulomatosis with polyangiitis (Wegener’s).

2.7.8 Local Steroid Injections

A granulomatous lesion of the nasal mucous membranes occurs in patients treated with injections of steroid preparations [108]. 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 microorganisms.

2.8 Benign Epithelial Neoplasms

2.8.1 Sinonasal Papillomas

Sinonasal papillomas are usually divided into squamous cell papilloma of the nasal vestibule and Schneiderian papillomas of the nasal cavity and paranasal sinuses (Table 2.2). The first are covered by the epithelium of the skin surface. The latter are lined by the respiratory mucosa of the nasal cavity and paranasal sinuses (referred to as the Schneiderian membrane) and comprise three histopathological types: exophytic, inverted, and oncocytic.

| Location         | Squamous | Everted | Inverted       | Oncocytic          |
|------------------|----------|---------|----------------|-------------------|
| Growth           | Exophytic| Exophytic| Endophytic-exophytic | Exophytic-endophytic |
| Epithelium       | Keratinizing squamous | Non-keratinizing squamous and ciliated | Non-keratinizing squamous and ciliated | Oncocytic columnar |
| Intraepithelial mucin cysts | − | + | + | +++ |
| Recurrence       | Unusual  | Usual*  | Usual*         | Usual*            |
| Malignancy       | Unusual  | Unusual | 10%            | <10%              |

Modified from Wenig [567]

*a*If incomplete excision
and oncocytic. The histopathologic features that clearly differentiate between the three types of Schneiderian papillomas have been well documented [109]. Human papillomavirus (HPV) types 6 and 11 are involved in the pathogenesis of exophytic papillomas but not so consistently in the other two variants of Schneiderian papillomas [110–112]. All oncocytic papillomas examined have been HPV negative [110, 112, 113].

2.8.1.1 Squamous Cell Papilloma of the Nasal Vestibule

**Definition** A benign proliferative lesion composed of delicate stromal papillae covered by squamous epithelium. Squamous cell papillomas (SCPs) located in the nasal vestibule are formed by keratinizing stratified squamous epithelium of the skin surface [114].

**Microscopy** SCPs 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 keratinization are present and hyperkeratosis, parakeratosis, or both may be seen (Fig. 2.25).

**Differential diagnosis** SCP of the nasal vestibule must be distinguished from exophytic papilloma of the Schneiderian mucosa. The keratinizing nature of the squamous epithelium in the former and the presence of mucous epithelial cells in the latter are the key differentiating features.

**Treatment and prognosis** SCPs of the nasal vestibule are benign, rarely recur after simple excision, and in general are not associated with HPV.

2.8.1.2 Everted (Schneiderian) Papilloma

**Definition** Everted (Schneiderian) papilloma (ESP) is composed of papillary fronds with delicate fibrovascular cores covered by multiple layers of epithelial cells.

**Synonyms** ESP is also known as exophytic, fungiform, septal, and transitional cell papilloma among other terms [115]

**Epidemiology** ESPs arise most frequently at the nasal septum and only very rarely in the lateral nasal walls or in paranasal sinuses [115]. Males are predominantly affected. Patients tend to be younger than with other types of Schneiderian papillomas. ESPs are almost always unilateral [116]. No side is preferred and bilaterality is exceptional.

**Macroscopy** ESP is a single, warty tumor measuring up to 1.5 cm in diameter.

**Microscopy** ESP is composed of branching papillary structures, with papillae covered by stratified non-keratinizing squamous epithelium, admixed with intermediate or transitional cells and with ciliated respiratory epithelium that contains interspersed mucin-secreting cells (Fig. 2.26). The supporting stroma is fibrovascular.
Differential diagnosis  The two main differential diagnoses of ESP are inverted papilloma and oncocytic papilloma. Neither the invaginated pattern of growth of inverted papillomas nor the oncocytic columnar epithelium of oncocytic papilloma is found in exophytic papilloma [109]. Non-keratinizing squamous cell carcinoma can be easily ruled out by the lack of atypia and invasion.

Treatment and prognosis  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 ESP.

2.8.1.3 Inverted (Schneiderian) Papilloma
Definition  Inverted (Schneiderian) papilloma (ISP) is a papilloma in which the epithelium invaginates and proliferates inward the underlying stroma.

Synonyms  Inverting papilloma [115]

Epidemiology and pathogenesis  ISP is the most common type of Schneiderian papilloma and accounts for about 60% of them [117]. 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 [115]. Patient's age ranges between 30 and 50 years and the male to female ratio is 3:1 [118]. Molecular studies show supportive evidence of clonality in ISPs [119].

Macroscopy  ISPs frequently have a polypoid appearance and may be grossly indistinguishable from nasal polyps of the common type.

Microscopy  ISPs are characteristically composed of invaginating crypts, cords, and nests covered by non-keratinizing squamous epithelium, which alternates with columnar ciliated respiratory epithelium and with intermediate or transitional epithelium. This newly formed duct system is similar to the embryonic development of the nasal mucosa [120]. The multilayered epithelium typically contains mucous cells and mucin-filled microysts. 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 [121]. An inverted growth is the hallmark of inverted papilloma, but varying degrees of papillary growth may be seen at the surface (Fig. 2.27) [116]. The surface is characteristically lined by respiratory type of epithelium; nevertheless, foci of surface keratinization are occasionally present [114]. 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 edematous 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 of the respiratory epithelium (Fig. 2.28). Seromucinous glands are absent, but branching gland ducts are often present. The tumor grows by extension to involve the contiguous sinonasal epithelium [122].

Differential diagnosis  ISPs must be distinguished mainly from REAH and from squamous cell carcinoma with basaloïd features.
Treatment and prognosis If treated only by local surgical excision, recurrence occurs in up to 75% of cases. Therefore, lateral rhinotomy and medial maxillectomy are advisable for tumors of the lateral nasal wall [123]. Carcinoma develops in about 10–15% of inverted papillomas [114, 123, 124]. Carcinoma may coexist with inverted papilloma at the initial presentation or originate subsequently [114, 122, 125–127]. According to the experience of Michaels and Heliquist [128], carcinoma does not usually develop in the course of recurrences of inverted papilloma. The presence of severe atypia or marked keratinization in an inverted papilloma is always suspicious of malignant transformation. In these instances, the entire specimen should be thoroughly examined to exclude an associated carcinoma. Most associated carcinomas are squamous and less often undifferentiated (Figs. 2.29 and 2.30) [129]; other types may also occur such as verrucous carcinoma [130]. Carcinoma associated with ISP has a 60% 10-year survival rate [131].

2.8.1.4 Oncocytic (Schneiderian) Papilloma
Definition Oncocytic (Schneiderian) papilloma (OSP) is papilloma composed of both exophytic fronds and endophytic invaginations lined by multiple layers of columnar cells with oncocytic features.

Synonyms OSP is also known as “columnar” or “cylindrical” cell papilloma [115]

Epidemiology OSP is the least common type of Schneiderian papillomas. It comprises less than 5% of all sinonasal papillomas [109, 114, 132–135]. Both sexes are equally affected. Bilaterality has not been documented.

Macroscopy Tumors are in general small, although occasionally may reach various centimeters in greatest dimension.

Microscopy OSPs 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 [136]. 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 tumor resembles inverted papilloma in its sites of occurrence, the lateral wall of the nasal cavity and the maxillary antrum.

Differential diagnosis OSP must be distinguished from low-grade mucoepidermoid adenocarcinoma and other low-grade adenocarcinomas of the sinonasal tract. Rhinosporidiosis is the main entity to rule out in endemic countries like India and South America, as sporangia of Rhinosporidium seeberi may mimic the microcysts of OSP.

Treatment and prognosis The same treatment principles apply for OSP as for ISP [134]. The rate of recurrence of OSP is considered to be 36%, which is slightly lower than in inverted papilloma. The low frequency of these tumors makes it difficult to evaluate its true malignant potential, which seems to be similar to that of inverted papilloma [133]. Atypical hyperplasia and carcinoma in situ changes can be occasionally found (Fig. 2.31). 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 [114, 132, 137–139].
2.8.2 Salivary Gland-Type Adenomas

2.8.2.1 Pleomorphic Adenoma

Definition Pleomorphic adenoma is a tumor composed of epithelial and modified myoepithelial cells variably mixed with mucoid, myxoid, or chondroid ground substance. Pleomorphism is architectural while cells are monomorphic.

Synonym Mixed tumor

Epidemiology Pleomorphic adenoma is the most frequent benign glandular tumor of the sinonasal region. Most of them arise on the nasal septum and the rest on the lateral nasal wall or turbinates. Origin from the maxillary antrum is rare. Most patients are between 20 and 60 years of age [140, 141].

Macroscopy Tumors are usually polypoid and may measure up to 5 cm.

Microscopy They are unencapsulated. Myoepithelial cells, often of the plasmacytoid hyaline type, tend to predominate over the glands [141].

Differential diagnosis Myoepithelioma is the main type of tumor to differentiate from pleomorphic adenoma.

Treatment and prognosis Wide surgical excision is recommended. The recurrence rate of sinonasal pleomorphic adenoma is much lower than for its counterpart in the major salivary glands [140, 142].

2.8.2.2 Other Salivary Gland-Type Adenomas

Rare examples of sinonasal oncocytoma have been reported, most arise from the nasal septum, although they may also arise from the maxillary sinus [143, 144]. Those examples that have behaved aggressively are more appropriately considered low-grade adenocarcinomas rather than adenomas [141]. Intranasal basal cell adenoma has been also documented [145]. In addition, myoepithelioma [146] and one case of sinonasal myoepithelioma transformed into myoepithelial carcinoma following multiple recurrences were reported [147].

2.8.3 Pituitary Adenomas

Definition Pituitary adenomas are benign tumors expressing the phenotype of cells of the anterior pituitary gland.

Epidemiology The rare pituitary adenomas of the sinonasal region are in most instances extensions from intrasellar tumors [148, 149]. Very unusually, they arise from ectopic pituitary tissue as tumors from the sphenoid sinus or the nasal cavity [150, 151].

Microscopy Extrasellar pituitary adenomas are histologically similar to tumors within the sella [148, 149]. The main growth patterns are diffuse, ribbonlike, papillary, and pleomorphic. Most consist of chromophobe cells (Fig. 2.32). Immunohistochemistry is required for classification according to the hormones produced [152].

Differential diagnosis Main pitfalls to avoid in pituitary adenomas presenting as sinonasal tumors include carcinoma, melanoma, paraganglioma, and olfactory neuroblastoma [152, 153].

Treatment and prognosis Complete surgical removal of pituitary adenomas is mandatory. Radiotherapy is required in incomplete resections as well as an optional dopamine agonist.

2.8.4 Primary Sinonasal Ameloblastoma

Definition Ameloblastoma (AMB) primary of the sinonasal tract is a tumor derived from remnants of odontogenic epithelium, having similar features to its gnathic counterparts (see Chap. 4) and devoided of significant osseous involvement [154].

Epidemiology Primary sinonasal AMBs are rare tumors that present in the nasal cavity and in the maxillary sinus [154–159]. The mean age of patients at presentation is about 60 years; the rate of men versus women is of 4 to 1 [154].

Macroscopy Frequently presents as a polypoid mass of variable size and rubbery consistence.

Microscopy AMB consists of centrally placed islands and nests of epithelial stellate reticulum cells, surrounded by columnar ameloblastic epithelium. The columnar epithelium presents a characteristic nuclear palisading with reverse
Due to the presence of cytoplasmic subnuclear vacuoles that displace the nuclei away from the basement membrane toward the stellate reticulum. Occasional foci of squamous metaplasia may be found in the stellate reticulum. Immunostaining for calretinin is positive in over 90% of AMB [160]. Remnant bands of covering respiratory epithelium may be found, which have been considered as a possible source of the tumor [154].

Differential diagnosis AMB must be distinguished mainly from basal cell adenoma, pleomorphic adenoma, basaloid squamous cell carcinoma, adenoid cystic carcinoma, and biphasic synovial sarcoma. Unicystic AMB must be told apart from odontogenic keratocyst (Fig. 2.33).

**Treatment and prognosis** Excellent results are usually achieved after surgical excision with margins free of tumor. Ameloblastoma is a benign, but locally aggressive tumor that requires long-term follow-up to control the risk of recurrence.

### 2.9 Benign Sinonasal Soft Tissue and Neural Neoplasms

#### 2.9.1 Hemangiomas

Hemangiomas of the upper respiratory tract may be of the lobular capillary, cavernous or venous types [161].

**2.9.1.1 Lobular Capillary Hemangioma**

**Definition** Lobular capillary hemangioma (LCH) is a benign proliferation of capillary blood vessels adopting a lobular configuration [161].

**Synonym** Pyogenic granuloma.

**Epidemiology and pathogenesis** The sinonasal mucosa accounts for 29% of the LCH of the upper aerodigestive tract. Although the cause of LCH is unknown, it has an association with trauma, pregnancy, and oral contraceptives [161].

**Clinical features** The nasal and the vestibular septum are typical sites for LCH. Nasal obstruction and epistaxis are the most common early symptoms.

**Macroscopy** LCHs present as red-colored polypoid formations with a collar-like invagination around its basis. They measure up to 1.5–2 cm.

**Microscopy** LCH consists of lobular arrangements of blood-filled capillaries separated by loose connective tissue. The blood supply is provided by a feeder vessel with branches ramifying to the lobules (Fig. 2.34). Nasal LCHs are covered often by squamous metaplastic epithelium. Superficial stromal edema and ulceration are common accompanying features. At the ulcerated zone, conventional granulation tissue may be found.

**Differential diagnosis** LCH should be distinguished mainly from conventional polypoid granulation tissue, which has a distinctive radial distribution of capillary blood vessels and lacks lobular arrangements. Other differential diagnoses include papillary endothelial hyperplasia, angiomyoid polyp, bacillary angiomatosis, glomangiopericytoma, Kaposi’s sarcoma, and angiosarcoma.

**Treatment and prognosis** After complete excision, recurrences of LCH are rare.
2.9.1.2 Cavernous Hemangioma

**Definition** Cavernous hemangiomas are neoplastic proliferations of thin-walled blood vessels with marked luminal dilatation.

**Epidemiology** Cavernous hemangiomas of the sinonasal tract are commonly intraosseous or involve the turbinates or the lateral nasal wall. They occur mainly in men in the fifth decade of life [163].

**Microscopy** As elsewhere in the body, they are composed of multiple, large thin-walled, dilated blood vessels separated by fibrous stroma (Fig. 2.35).

**Differential diagnosis** Cavernous hemangioma of the sinonasal tract has to be distinguished from venous hemangioma, a rare vascular tumor in this location being composed of thick-walled veins with abundant smooth muscle. Other differential diagnoses include sporadic telangiectasia, hereditary telangiectasia (Osler-Weber-Rendu syndrome), vascular malformations, angiomatoid polyps, and papillary endothelial hyperplasia.

**Treatment and prognosis** Complete removal is the treatment of choice whenever possible. Recurrences occur after incomplete resection.

2.9.2 Fibroma and Fibrous Histiocytoma

2.9.2.1 Fibroma

**Definition** Sinonasal fibroma is a benign nodular proliferation composed of fibroblasts and collagen.

**Epidemiology and pathogenesis** Sinonasal fibromas are uncommon lesions, mainly seen in the nasal cavity. Their distinction from reactive fibrosis may be controversial. A few true examples reported in the past [164] continue to be recognized as such nowadays [165].

**Macroscopy** Sinonasal fibromas are small nodules of polypoid configuration that may measure up to 1 cm.

**Microscopy** They consist of a proliferation of fibroblastic spindle cells intermingled with bands of collagen. Cytoplasms are inconspicuous and nuclei are bland, although on occasions may depict slight pleomorphism. Mitoses are minimal or absent (Fig. 2.36).

**Differential diagnosis** Sinonasal fibromas must be distinguished from other benign sinonasal myofibroblastic proliferations. True sinonasal fibromas are only immunoreactive for vimentin.

**Treatment and prognosis** Complete removal is curative.

2.9.2.2 Fibrous Histiocytoma

**Definition** Benign fibrous histiocytoma (BFH) is a benign nodular proliferation composed of fibrohistiocytes and collagen.

**Epidemiology** Since the advent of immunohistochemistry, tumors typed as sinonasal BFHs have become an exceedingly rare entity.

**Clinical features** BFH presents as a yellow-tan nodule or polyp, most commonly causing nasal obstruction or bleeding [165].
Microscopy BFH is composed of spindle-shaped cells arranged in a storiform pattern admixed with histiocytic cells and multinucleated giant cells.

Differential diagnosis The distinction from other benign sinonasal spindle cell proliferations is largely based on the immunohistochemical findings. BFH is immunoreactive for vimentin and for markers of macrophages such as CD68.

Treatment and prognosis Benign fibrous histiocytoma may recur if incompletely excised.

2.9.3  Leiomyoma and Myofibroma

2.9.3.1  Leiomyoma
Definition Leiomyoma is a benign nodular proliferation composed of smooth muscle cells.

Epidemiology Sinonasal leiomyomas are rare tumors. They occur in adults and preferentially involve the nasal cavities [166].

Clinical features Nonspecific symptoms of nasal obstruction [166].

Microscopy Their morphologic and immunohistochemical profiles are identical to those of leiomyomas of other sites. An origin from blood vessel walls has been postulated. Leiomyomas usually express smooth muscle actin, muscle-specific actin, and desmin.

Differential diagnosis The distinction of leiomyoma from myofibroma is mainly based on immunohistochemical features and on the presence in the latter of a hemangiopericytoma-like vascular network, which is lacking in the former (see also Sect. 2.9.3.2). The distinction of leiomyoma from leiomyosarcoma is based on the absence of atypia and mitoses in the former.

Treatment and prognosis Complete removal of leiomyomas is curative. Huang and Antonescu have proposed to separate a category of smooth muscle tumors of uncertain malignant potential, characterized by the presence of 1–4 mitotic figures/10 high-power fields, which tend to pursue a more aggressive behavior than leiomyoma [167].

2.9.3.2  Myofibroma
Definition Myofibromas are solitary nodular proliferations composed of benign myofibroblasts. Myofibromatosis is the term for the presence of multiple myofibromas.

Epidemiology Most myofibromas are seen in young children. Sinonasal myofibromas are very rare [168].

Microscopy Myofibromas are made up of interlacing fascicles of plump spindle cells, with weakly eosinophilic cytoplasm and bland, round to oval nuclei. The cellular density may vary between the different areas. In the densely cellular areas, the blood vessels may show hemangiopericytoma-like features [169]. Myofibromas express smooth muscle actin and muscle-specific actin and are usually negative for desmin and other markers [170].

Differential diagnoses Sinonasal myofibromas must be differentiated from leiomyomas, as well as from glomangiopericytoma and low-grade myofibroblastic sarcoma.

Treatment and prognosis Complete excision of myofibromas is the recommended treatment. Incompletely removed tumors may recur.

2.9.4  Schwannoma, Neurofibroma, and Neurothekeoma

2.9.4.1  Schwannoma
Definition Schwannoma is a benign tumor, composed of differentiated, neoplastic Schwann cells [162].

Synonym Neurilemmoma

Epidemiology About 4% of schwannomas of the head and neck region arise in the sinonasal tract [163]. Schwannomas of the sinonasal mucosa are usually not associated with type 2 neurofibromatosis.

Clinical aspects They usually present as polypoid lesions involving the nasal cavity and/or a paranasal sinus, with nonspecific symptoms of obstruction, compression, or extension in the surrounding structures [162].
Microscopy  Histologically, the tumor 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, while mitotic activity is absent to low. A consistently reported feature of sinonasal schwannomas is the lack of tumor encapsulation which determines an apparently infiltrative growth pattern. Immunohistochemically, sinonasal schwannoma is intensely reactive for S-100 protein and also for vimentin [171].

Differential diagnosis  It includes neurofibroma and other spindle cell lesions of the sinonasal mucosa, like angiofibroma, solitary fibrous tumor, and leiomyoma. Particular care should be taken in evaluating cellular schwannomas with a predominance of Antoni type A areas, which should not be confused with malignant spindle cell neoplasms, like malignant peripheral nerve sheath tumor, fibrosarcoma, leiomyosarcoma, and spindle cell melanoma.

Treatment and prognosis  Complete removal of sinonasal schwannomas is curative.

2.9.4.2 Neurofibroma
Definition  Neurofibroma is a benign tumor of peripheral nerve sheath phenotype with mixed cellular components including Schwann cells, perineural hybrid cells, and intraneural fibroblasts [162].

Epidemiology  Neurofibromas of the sinonasal mucosa are rare, usually solitary, and sporadic, not associated with multiple neurofibromatosis, type 1 (von Recklinghausen’s disease).

Etiology and pathogenesis  Experimental induction of peripheral nerve sheath tumors of the Gasserian ganglion and the orbital and maxillary regions has been achieved after prenatal and postnatal exposure to ethylnitrosourea [172].

Microscopy  Neurofibromas appear as unencapsulated lesions composed of a mixture of Schwann cells and fibroblasts embedded in a predominately myxoid stroma. Residual neurites may be found at the center of the lesion [162, 173].

Differential diagnosis  Due to the overlap of the histological features, it may be difficult to differentiate neurofibroma from schwannomas of the sinonasal mucosa. Neurofibroma should be distinguished also from myxoma, which is S-100 protein negative.

Treatment and prognosis  Complete removal is the treatment of choice for solitary neurofibroma.

2.9.4.3 Neurothekeoma
Definition  Neurothekeoma is a rare benign neoplastic proliferation derived from nerve sheaths and arranged in lobules separated by fibrous septa.

Epidemiology  The tumor may be seen anywhere in the body. One neurothekeoma of the paranasal sinuses has been reported in a 3-year-old boy [174].

Microscopy  A syncytium of spindle and epithelioid-like cells often admixed with osteoclastoid cells and occasional myxomatous areas appears surrounded by fibrous septations that confer the lobular pattern. Tumor cells are usually positive for vimentin and glial fibrillary acidic protein, while reactivity for S-100 protein is variable. Cytokeratin markers are constantly negative.

Treatment and prognosis  Complete resection is curative.

2.9.5 Meningioma
Definition  Meningioma is a tumor derived from meningotheelial cells.

Epidemiology  Meningiomas of the sinonasal tract may extend directly from the central nervous system or arise from ectopic extracranial tissue. Although rare, they are more commonly seen in the orbit, ear, and skin of the head and neck than in the sinonasal tract. Sinonasal meningiomas tend to occur in younger patients than intracranial meningiomas [162, 175].

Microscopy  Histologically, they are similar to meningiomas elsewhere, being the meningotheelial type the most frequent. Aggressive variants of meningioma may be seen mainly within the group of primary intracranial sinonasal meningiomas.

Treatment and prognosis  Surgical removal with margins free of tumor is mandatory. Extracranial sinonasal meningiomas have usually an excellent prognosis. Primary intracranial sinonasal meningiomas require aggressive surgery [176].

2.9.6 Juvenile Angiofibroma
Definition  Juvenile angiofibroma (JAF) is a benign and richly vascularized fibrous neoplasm that arises in the posterior nasal cavity and neighboring nasopharynx in young males [177].

Synonym  Nasopharyngeal angiofibroma
Epidemiology JAF arises in the confluence of the postero-lateral nasal wall and the lateral nasopharynx and occurs nearly always in young males [177, 178]. Although JAFs almost invariably arise in the nasopharynx and often extend secondarily to the sinonasal region, about 1.5% of angiofibromas involve the nasal cavity alone [179].

Clinical aspects Although benign JAF 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, into the orbit, and intracranially.

Macroscopy JAFs are sessile or polypoid lobulated formations of rubbery consistency, well demarcated but devoid of a capsule (Fig. 2.37). The cut surface is whitish and a rich vascularization is not always apparent.

Microscopy JAFs are composed of vascular and fibrous elements in varying proportions. The vessels in the superficial portions of the tumor are mainly gaping capillaries which 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 tumor. 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 collagenization. Stellate fibroblast-like cells are often present close to the blood vessels. The tumor cells express vimentin and the vascular endothelial cells CD31 and CD34. Pericytes that surround parts of small blood vessels stain for smooth muscle actin. The nuclei of fibroblastic cells of juvenile angiofibroma are strongly positive for testosterone receptors [180]. Ultrastructurally the nuclei of angiofibroma contain characteristic dense granules [181]. Occasionally, the fibroblasts may exhibit cytologic atypia, and some of these cells may be multinucleated, but mitosis are rare. Mast cells may be numerous. There may be focal thrombosis, hemorrhage, and chronic inflammatory reaction. With the advent of preoperative selective embolization, iatrogenic emboli may be encountered in resected specimens (Fig. 2.38) [182]. For further reading on this tumor, see Chap. 6.

2.10 Borderline Soft Tissue Neoplasms

2.10.1 Glomangiopericytoma

Definition Glomangiopericytoma (GPC) is a sinonasal tumor with perivascular myoid phenotype, showing features of glomus and pericytes [183, 184]. It is characterized by the proliferation of oval, polyhedral, or spindle-shaped cells arranged about vascular channels provided with a single layer of endothelial cells [185, 186].

Synonyms Hemangiopericytoma-like tumor, sinonasal hemangiopericytoma, and sinonasal glomus tumor

Epidemiology GPCs arise in the nasal cavity as well as in the paranasal sinuses. They show a slight predilection for females. Most of them develop in the seventh decade of life.

Clinical features Nasal obstruction, epistaxis, and difficulty of breathing are usual presenting symptoms. A rare association with osteomalacia has been recently reported [187, 188].
**Macroscopy**  GPCs are usually polypoid measuring in average 3 cm and may reach up to 8 cm in size [189].

**Microscopy**  GPC contains numerous thin-walled blood vessels that often may adopt a staghorn configuration and on occasions are surrounded by prominent hyalinization. The tumor cells, typically arranged around the blood vessels, are of uniform size with regular oval or elongated nuclei and pale cytoplasm; mitoses are very rare and without atypia (Fig. 2.39). 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 tumor cells are enmeshed by collagen type IV fibers and entirely situated outside the capillaries which are lined by a single-layer of normal-looking endothelium.

**Immunohistochemistry**  GPCs show diffuse reactivity for actins, factor XIIIa, and vimentin, lacking diffuse staining for other markers. GPC vessels stain for muscle-specific actin [184].

**Differential diagnosis**  It includes lobular capillary hemangioma, solitary fibrous tumor, leiomyoma, myofibroblastic low-grade sarcoma, synovial sarcoma, and leiomyosarcoma [184]. In GPC the tumor cells are enmeshed by collagen type IV fibers; this feature, well shown by reticulin stain or by anti-collagen IV antibodies, helps to distinguish the tumor from angiosarcoma [184]. In due clinical settings, other differential diagnoses to consider are Kaposi’s sarcoma and phosphaturic mesenchymal tumor.

**Treatment and prognosis**  Complete surgical removal is the recommended treatment for GPCs achieving an overall 5-year survival of about 90%; recurrence may occur many years after initial surgery and may rarely metastasize [184, 189]. Aggressive GPCs (malignant glomangiopericytomas) are very uncommon and often show size larger than 5 cm, bone invasion, nuclear atypia, necrosis, increased mitotic number, and proliferation index higher than 10% [184, 189, 190].

### 2.10.2 Desmoid-Type Fibromatosis

**Definition**  Desmoid-type fibromatosis (DTF) is a nonmetastasizing unencapsulated myofibroblastic proliferation that has a tendency for local invasion and recurrence.

**Synonyms**  Desmoid tumor, extra-abdominal fibromatosis, and aggressive fibromatosis

**Epidemiology**  DTF rarely arises in the sinonasal tract [164, 191].

**Microscopy**  DTF is composed of interlacing fascicles of bland spindle-shaped myofibroblasts, in a collagenous background of parallel-running fibers. Focal myxoid areas may be found. Immunohistochemistry: Actins and vimentin are positive while desmin only occasionally. Beta-catenin presents intranuclear localization [192].

**Differential diagnosis**  DTF must be distinguished from fibrosarcoma, solitary fibrous tumor, fibroma, and reactive types of fibrosis.

**Treatment and prognosis**  Complete surgical removal is the treatment of choice; positive or close (<1 mm) resection margins are predictive of recurrences [193]. DTFs of the sinonasal tract tend to have lower recurrence rates than those arising in other locations [164].

### 2.10.3 Solitary Fibrous Tumor

**Definition**  Solitary fibrous tumor (SFT) of the nose and paranasal sinuses is a fibroblastic proliferation with variable cellularity and vascularity having features identical to those of SFT of the pleura [194–196].

**Epidemiology**  The sinonasal region is the second most common location for SFTs of the upper aerodigestive tract, only preceded by the oral cavity. SFTs mainly develop in adults, with slight predominance in women [194–198].
Clinical features Nasal obstruction is the most common presenting symptom.

Macroscopy Sinonasal SFTs are polypoid to nodular formations of firm consistency that usually measure several centimeters [199].

Microscopy SFTs are characterized by a disorderly proliferation of small spindle cells with bland nuclei and inconspicuous cytoplasm that produce abundant amounts of collagen (Fig. 2.40). The proportion of cells and collagen may vary considerably between the different areas. Mitoses are quite uncommon; growth is slow and expansile. Usually vascularization is prominent with blood vessels forming thick collagenized walls; in other areas hemangiopericytoma-like vessels may be found. Mucosal ulceration, necrosis, and invasion are usually absent. Nevertheless, recent examples of malignant SFTs of the upper aerodigestive tract have been reported [200].

Immunohistochemistry SFTs are immunoreactive for CD34, BCL2, CD99, and vimentin [195].

Differential diagnosis The main differential diagnoses of SFT are sinonasal glomangiopericytoma and juvenile angiofibroma. Also, other benign and malignant spindle cell tumors must be distinguished from SFT.

Treatment and prognosis Fully excised SFTs with free margins do not recur. This is the case for sinonasal polyoid SFTs. Broad-based SFTs are difficult to remove and prone to recur. Progression of recurrences is in most cases very slow [199]. The very rare examples of malignant SFT behave aggressively [200].

2.11 Malignant Neoplasms

Malignant sinonasal tumors comprise less than 1% of all cancers seen in humans and represent about 3% of all malignancies of the head and neck region [201, 202]. Despite the low rate of malignancy arising in the sinonasal tract, a great variety of histological types of tumors may be found [121, 122]. The advent of electron microscopy and the more recent advances in immunohistochemistry, and in gene technologies, have further refined the criteria for their correct recognition [203], which recent comprehensive publications have made available worldwide [204, 205].

Geographical differences in the relative frequency of certain histological types of malignant sinonasal tumors may be related to variations in the exposure to carcinogens [206]. In Table 2.3, the histological types of malignant sinonasal tumors collected at the Hospital Clinic of the University of Barcelona from 1976 to 2005 are presented in decreasing order of frequency. Keratinizing squamous cell carcinoma, undifferentiated carcinoma, non-keratinizing squamous cell carcinoma, malignant lymphoma, malignant mucosal melanoma, intestinal-type adenocarcinoma, adenoid cystic carcinoma, low-grade adenocarcinomas, and olfactory neuroblastoma are the most frequent histological types. Most common sinonasal carcinogens in humans are cigarette smoking, high-risk HPV, radiation therapy, nickel, chromates, wood dust, boot and shoe dusts, and isopropyl alcohol.

A practical way to start typing malignant sinonasal tumors is to separate them into large and small cell categories. Among the large cell malignant tumors, the most common types are squamous cell carcinoma, non-keratinizing squamous cell carcinoma, malignant mucosal melanoma, intestinal-type adenocarcinoma, and low-grade adenocarcinomas. Sinonasal undifferentiated carcinoma, malignant lymphoma, adenoid cystic carcinoma, and olfactory neuroblastoma are among the most common small cell tumors. Large cell tumors account for approximately 75% of the malignant sinonasal tumors and the small cell tumors for the remaining 25%.

For staging of malignant sinonasal tumors, Ref. [207] is recommended, as well as Tables 13 and 14 in Chap. 17.

2.11.1 Keratinizing Squamous Cell Carcinoma

Definition Keratinizing squamous cell carcinoma (KSCC) is a malignant epithelial neoplasm originating from the mucosal epithelium of the nasal cavities or paranasal sinuses with histological evidence of squamous differentiation and keratin production.
**Synonyms** Conventional squamous cell carcinoma and squamous cell carcinoma NOS

**Epidemiology** At the nasal vestibule, KSCC is the most common malignancy [208–210]. Due to early recognition and easy access to treatment, they usually have more favorable prognosis than their counterpart of the sinonasal region.

Sinonasal KSCC comprises up to 45–50% of the malignant tumors of this region in several series [211, 212]. 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 ethmoid sinuses are the most common sites (Fig. 2.41) [213]. Other locations such as the nasal septum and the nasal floor are less usual; the frontal and sphenoid sinuses are rarely involved. These tumors grow by local extension, infiltrating the neighboring structures, but lymph node metastases are rare [214].

**Etiology and pathogenesis** The occupational epidemiology of KSCC has been strongly related to exposure to nickel [215–218] and to a lesser extent to chromium, isopropyl alcohol, and radium [219]. As in other territories of the respiratory tract, a definite association between sinonasal KSCC and cigarette smoking has been documented [220, 221]. Chronic sinonasal inflammation is considered as a predisposing factor. A case of carcinoma of the maxillary antrum after thorotrast exposure has been reported [222].

| Table 2.3 Malignant sinonasal tumors at the Hospital Clínic, University Barcelona Medical School |
|------------------------------------|----------------|---|---|---|---|
| Type of tumor | Frequency | Men | Women | Mean | Age | Range |
| Keratinizing SCC | 54 | 27 | 38 | 70 | 16 | 30 | 64 | 39–87 |
| Undifferentiated carcinoma | 26 | 13 | 19 | 73 | 7 | 27 | 60 | 41–87 |
| Non-keratinizing SCC | 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 |

Fig. 2.41 Main locations of sinonasal malignant tumors: 1 maxillary sinus, 2 ethmoid and lateral wall, 3 nasopalatine septum, 4 nasal septum, and 5 roof of the nasal cavity (Courtesy of Prof. J Traserra, Barcelona, Spain. Ref: [213])

Nitrosamines and to a lesser extent formaldehyde are strong nasal carcinogens in laboratory rodents [223, 224].
Macroscopy
Sinonasal KSCCs display gross features similar to those of other upper aerodigestive tract territories.

Microscopy
KSCCs originate in the respiratory sinonasal mucosa from areas of preexisting squamous metaplasia and manifest the same range of histological appearances as those arising in other sites. They are characterized by the proliferation of malignant squamous epithelial cells with keratin production and intercellular bridges (Fig. 2.42). 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. Most KSCC of the sinonasal tract present as moderately or poorly differentiated tumors. Special types of squamous cell carcinoma (SCC), such as verrucous carcinoma [225], spindle cell carcinoma [226, 227], basaloid squamous cell carcinoma [228, 229], and adenosquamous carcinoma [230, 231], are occasionally found in the sinonasal tract.

Immunohistochemistry and in situ hybridization
The prototypical KSCC is p53 positive, p16 negative, and high-risk HPV negative.

Differential diagnosis
KSCC has to be mainly differentiated from NKSCC and from other special types of SCC. Well-differentiated carcinomas are uncommon in this territory and when encountered need to be differentiated from pseudoepitheliomatous types of hyperplasia and from verrucous carcinoma.

Treatment and prognosis
Complete surgical resection combined with radiotherapy and optional chemotherapy is recommended [232, 233]. Regional lymph node involvement is seen in about 17% of sinonasal squamous cell carcinomas and distant metastases in about 1.5% [214]. For neoplasms circumscribed to the nasal cavity, the 5-year survival is slightly above 50% [234], whereas in neoplasms of the maxillary antrum, the 5-year survival may be as low as 25% [220].

2.11.2 Non-keratinizing Squamous Cell Carcinoma

Definition
Non-keratinizing squamous cell carcinoma (NKSCC) is a malignant epithelial neoplasm originating from the mucosal epithelium of the nasal cavities or paranasal sinuses with squamous differentiation and lack of histological evidence of keratin production.

Synonyms
Cylindrical cell carcinoma, transitional cell carcinoma, and Schneiderian carcinoma. The name cylindrical cell carcinoma was first coined by Ringertz in 1938 [235]; it was the preferred term in the 1991 WHO classification [121], until the 2005 WHO classification recommended non-keratinizing squamous cell carcinoma as the most appropriate term [202].

Etiology and pathogenesis
NKSCC is etiopathogenetically related with HPV [236–238]. In SCC with biologically active HPV, inactivation of the Rb protein by the HPV E7 protein leads to p16 overexpression because Rb normally represses the transcription of p16. HPV-positive HNSCC also expresses the oncoprotein E6 that binds and degrades wild-type p53 protein [238]. Unlike carcinomas of the uterine cervix, where HPV infection and TP53 mutations are mutually exclusive events, HPV infection and TP53 overexpression sometimes occur together in HNSCC, but disruptive TP53 gene mutations are not encountered in HPV-positive carcinomas [239, 240].

Epidemiology
NKSCC affects males more often than women, at younger ages than keratinizing carcinoma, between 40 and 60 years of age, in patients that usually do not drink alcohol nor smoke tobacco [241, 242]. Twenty percent of sinonasal SCC is HPV positive and shows non-keratinizing histological features [236–238]. Eighty-two percent of them were type 16, 12% types 31/33, and 6% type 18 [243].

Macroscopy
The tumors grow in most cases as exophytic masses showing either corrugated or smooth surface. They may arise from the antrum, the lateral nasal wall, or the ethmoid, being the antrum the most frequent site. They may occur concomitantly with other nonneoplastic polypoid formations.

Microscopy
Main histological features of NKSCC are the presence of islands and interlaced cords of squamous epithelial cells with the lack of maturation, absence of keratinization, and moderate to significant degree of atypia (Fig. 2.43).
The tumor invades into the underlying fibrosed tissue with an expanding, smooth and lobulated, generally well-delineated border, although foci of infiltration by irregular small nests or strands may be seen. NKSCC is usually moderately or poorly differentiated, being in the latter case difficult to recognize as SCC. Occasionally, some degree of keratinization may be seen. When keratinization is conspicuous, there may be microscopic overlap with KSCC [202]. Some of these tumors may also overlap with the papillary, basaloid SCC, adenosquamous [244], and lymphoepithelial-like types of SCC.

The papillary variant of NKSCC is composed of papillary fronds, thick ribbons, and polystratified masses of commonly cylindrical cells that give rise quite often to invaginations of the surface epithelium [245]. The tumor cells have a tendency to form palisade arrangements perpendicular to the underlying basement membrane (Fig. 2.44). The nuclei are atypical and show increased mitotic activity, as well as abnormal mitotic figures. The basement membrane remains in most cases conspicuous, despite stromal infiltration, which should not be regarded as carcinoma in situ. Recent studies have shown that not only the papillary type but most of the variants of head and neck SCC may be associated with high-risk HPV [244, 246–248].

Immunohistochemistry  HPV-positive NKSCCs are immunohistochemically positive for p16 protein in a diffuse and intense fashion (Fig. 2.45). Positivity must be nuclear, although cytoplasmic positivity is also seen [236–238].

Molecular diagnosis  HPV detection may be achieved through various techniques [203], such as DNA-PCR [236] or DNA-ISH (Fig. 2.46) [237], as well as mRNA-PCR [238] or mRNA-ISH assays [249]; the latter have gained increasing relevance as it is not the presence of the virus alone but its transcriptional activity what confers pathogenicity. For a more detailed description of these methods, the reader is referred to Chap. 6.

Differential diagnosis  In addition to rule out KSCC and the different sinonasal SCCs that are negative for HPV, it includes 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 NKSCC. When Schneiderian papillomas coexist with NKSCC, or with other types of carcinoma, the two components appear usually demarcated one from the other although in contiguity. When the invaginating crypts of an inverted papilloma are filled with the cords and ribbons of a keratinizing or non-keratinizing SCC, the lesion represents a conventional squamous cell carcinoma arising in an inverted papilloma, which implies a worse prognosis than that of NKSCC.
An unusual variant of HPV-related carcinoma with adenoid cystic-like features arising in the sinonasal tract was recently described because of immunohistochemical p16 protein expression. It was characterized by a nested growth with a prominent basaloid component showing myoepithelial differentiation, microcystic spaces, and even ductal structures. Evidence of squamous differentiation, when present, was restricted to the surface epithelium [243]; more experience with this type of tumor may be needed to clearly separate it from the HPV-related basaloid SCC. A unique example of low-grade papillary Schneiderian carcinoma has been very recently reported [250].

Treatment and prognosis NKSCC behaves as locally aggressive tumor, and the recommended treatment is complete surgical excision followed by radiotherapy. NKSCC bears a better prognosis than conventional squamous cell carcinomas [236, 237, 251]. The mechanisms underlying this favorable outcome may involve the combined effects of immune surveillance to viral-specific tumor antigens, an intact apoptotic response to radiation, and absence of widespread genetic alterations associated with smoking [252–255].

2.11.3 Sinonasal Undifferentiated Carcinoma

Definition Sinonasal undifferentiated carcinoma (SNUC) is 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, as well as rosette formation [256–258].

Epidemiology etiology, and pathogenesis SNUC occurs in both sexes over a wide age range, with a median in the sixth decade of life. Cigarette smoking [257] and nickel exposure [218] 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 tumor (Table 2.4). Ionizing radiation is another etiologic factor, for radiotherapy either for retinoblastoma or for nasopharyngeal carcinoma has been associated with SNUC [259]. High-risk HPV has been recently related to SNUC [260].

Clinical aspects The most common symptoms are nonspecific and include nasal obstruction, proptosis, cranial nerve
palsies, periorbital swelling, diplopia, epistaxis, and periorbital pain [257]. Most tumors present in advanced stage with involvement of multiple paranasal sinuses and invasion of adjacent structures, including the orbit, the cranial cavity and the nasopharynx (Fig. 2.47).

**Macroscopy** The tumors are often extensive lesions.

**Table 2.4** Immunohistochemical and molecular features of SNUC

|                      |          |
|----------------------|----------|
| CK                   | ++       |
| EMA                  | +        |
| NSE                  | -        |
| Synaptophysin        | -        |
| Chromogranin         | -        |
| S-100 protein        | -        |
| HR-HPV               | +/-      |
| EBV                  | -        |
| del 13q14            | -        |
| Other markers        | -        |

**Microscopy** 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 moderate amount of either amphophilic or eosinophilic cytoplasm. Mitotic figures are common (Fig. 2.48). The tumor forms nests, cords, and sheets of cells that show frequent areas of central necrosis and tendency to vascular and perineural invasion (Fig. 2.49).

**Fig. 2.47** Sinonasal undifferentiated carcinoma: CT scan demonstrating bilateral occupation of the nasal cavity, perforation of the nasal septum, extensive involvement of paranasal sinuses, including left sphenoid and also the left orbit (Courtesy of Prof. J. Traserra, Barcelona, Spain)

**Fig. 2.48** Sinonasal undifferentiated carcinoma: interconnected nests of small- to medium-sized, polygonal undifferentiated epithelial cells with distinct borders. They show round to oval, hyperchromatic, or vesicular nuclei, surrounded by moderate amount of cytoplasm

**Fig. 2.49** Sinonasal undifferentiated carcinoma: nests of small to intermediate epithelial cells showing pleomorphic atypical nuclei, with either inconspicuous or slightly prominent nucleoli, mitosis, and areas of necrosis
Immunohistochemistry  SNUCs are immunoreactive with epithelial markers, such as simple epithelium-type cytokeratins (Fig. 2.50) [261] and epithelial membrane antigen (EMA). Synaptophysin, chromogranin, and other neuroendocrine markers are negative [262]. In a recent report, up to 47% of SNUCs have been found positive for high-risk HPV [260]. EBV is negative [256, 259] (Table 2.4).

Electron microscopy  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 either absent or very rarely found (Fig. 2.51).

Genetics  Few cases of SNUC have been examined cytogenetically, and they showed a complex karyotype [263]. Activating genomic mutations of clinically relevant genes, including AKT, BRAF, CDK4, CTNB1, EGFR, FBXW7, JAK2, c-KIT, KRAS, PDGFR, PI3K, and VEGF, have not been detected [264, 265].

Differential diagnosis  The three main differential diagnoses of SNUC are small cell neuroendocrine carcinoma (SCNC), large cell neuroendocrine carcinoma (LCNC), and high-grade olfactory neuroblastoma (ONB). All four entities may share some overlapping clinical and light microscopic features. However, SNUC, SCNC, and LCNC show a marked immunoreactivity for cytokeratins that is not seen in ONB, and on the other hand, SNUC lacks the marked neuroendocrine immunoreactivity seen in SCNC, LCNC, and ONB (Table 2.5). Most lesions categorized in the past as grade IV ONB are now considered to be either SNUC or SCNC. This is important because SNUC, SCNC, and LCNC have worse prognosis than ONB. The recently described NUT carcinoma can be separated from SNUC based on the presence of NUTM1 gene rearrangement or NUT immunohistochemical positivity. Notably, in the past, NUT carcinomas arising in the sinonasal tract may have been diagnosed as SNUC [266].

In addition, SNUC needs to be distinguished from other primary sinonasal tumors, such as solid adenoid cystic carcinoma, microcytic malignant melanoma, NKSCC, primary sinonasal nasopharyngeal-type undifferentiated carcinoma, lymphoma, and others.

Treatment and prognosis  SNUCs are very aggressive tumors, with frequent local recurrence and spread to lymph node and distant sites. In most instances, the tumor is so large and the infiltration is so extensive that complete surgical resection cannot be achieved. Neck involvement in advanced local disease is considered a poor prognostic sign [267]. Combined treatments, including surgery and adjuvant radiotherapy, or surgery, radiotherapy, and chemotherapy,

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**Fig. 2.50**  Sinonasal undifferentiated carcinoma: strong immune reaction of the tumor cells with the marker of low molecular weight cytokeratins CAM 5.2

**Fig. 2.51**  Sinonasal undifferentiated carcinoma: ultrastructurally, poorly formed desmosomes are seen joining the cells (Courtesy of Prof. J.A. Bombi, Barcelona, Spain)
### Table 2.5  Summary of the immunohistochemical and molecular features of selected sinonasal round cell tumors

| Entity                        | CK        | SYN       | CHR       | CD56      | S100      | HMB45     | CD45     | CD99     | Desmin   | P63       | Calretinin | EBV | Molecular diagnostics |
|-------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|----------|----------|----------|-----------|------------|-----|----------------------|
| Sinonasal undifferentiated carcinoma | 7+, 8+ | (focal +) | (focal +) | −         | −         | −         | −        | −        | −        | Rarely + | −          | −   |                      |
| Nasopharyngeal-type undifferentiated carcinoma | Pan+, 5/6+, 13+ | −        | −         | −         | −         | −         | −        | −        | +        | +         | +          | −   |                      |
| Neuroendocrine carcinoma      | Pan+, 5/6− | +        | +         | +         | −         | −         | −        | −        | −        | −         | −          | −   |                      |
| Nasopharyngeal-type undifferentiated carcinoma | Pan+, 5/6+, 13+ | −        | −         | −         | −         | −         | −        | −        | +        | −         | +          | −   |                      |
| Neuroendocrine carcinoma      | Pan+, 5/6+ | −        | −         | −         | −         | −         | −        | −        | −        | −         | −          | −   |                      |
| Nasopharyngeal-type undifferentiated carcinoma | Pan+, 5/6+, 13+ | −        | −         | −         | −         | −         | −        | −        | +        | −         | +          | −   |                      |
| Basaloid squamous cell carcinoma | Pan+, 5/6+ | −        | −         | −         | −         | −         | −        | −        | −        | −         | −          | −   |                      |
| NUT carcinoma                 | Pan+, 7+  | −        | −         | −         | −         | −         | −        | −        | +        | ND        | −          | t(15;19) |                      |
| Ectopic pituitary adenoma     | Pan+     | +        | +         | +         | −         | −         | −        | +        | −        | −         | −          | −   |                      |
| Olfactory neuroblastoma       | −        | +        | +         | +         | Sustentacular cells | −   | −       | −       | −       | −       | −       | −       |                      |
| Melanoma                      | − (rarely +) | − (rarely +) | − (rarely +) | − (rarely +) | + | + | − | − | (rarely +) | − | − (rarely +) | − |                      |
| Lymphoma                      | −        | −        | −         | + in NK/T cell | − | − | + | − | − | − | − | + in NK/T cell | − |                      |
| Rhadomyosarcoma                | − (rarely +) | − (rarely +) | − | − (rarely +) | − | − | − | − | − | − | − | − | − | − (rarely +) | − |                      |
| Ewing's sarcoma               | − (rarely +) | − (focal +) | − | − (focal +) | − (focal +) | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − (rarely +) | − | t(11;22) |
| Metastatic neuroblastoma       | −        | +        | +         | +         | −         | −         | −        | −        | −        | −         | −          | −   |                      |

*CK* cytokeratins, *SYN* synaptophysin, *CHR* chromogranin, *ND* not determined

*a* Lymphoblastic lymphoma and anaplastic large cell lymphomas are positive for CD99
seem to offer the best chance of cure compared with either modality alone [268, 269]. High-dose chemotherapy and autologous bone marrow transplantation have been considered as a form of treatment [270]. Prognosis of SNUC is dismal, with a median survival of 4 months to 1 year [257, 258]. In a recent meta-analysis of outcome, 26.3% of patients were alive with no evidence of disease, 21.0% were alive with disease, and 52.7% were dead of disease [267].

2.11.4 Primary Sinonasal Nasopharyngeal-Type Undifferentiated Carcinoma

Definition A poorly differentiated squamous cell carcinoma or histologically undifferentiated carcinoma accompanied by a prominent reactive lymphoplasmacytic infiltrate, morphologically similar to nasopharyngeal carcinoma, that originates in the sinonasal tract.

Synonym Sinonasal lymphoepithelioma.

Although nasopharyngeal carcinoma (NPC) almost invariably arises in the nasopharynx [271], “bona fide” primary sinonasal nasopharyngeal-type undifferentiated carcinomas (PSNPC) have been recently reported [259]. Due to the undifferentiated appearance of cells in NPC and PSNPC, these tumors may be lumped together with SNUC if unaware of their differences [256, 259, 261]. 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 tumors 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 situ hybridization 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 SNUCs 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. HPV-related lymphoepithelial-like NKSCC is another entity to be distinguished from PSNPC.

2.11.5 Neuroendocrine Neoplasms

Sinonasal neuroendocrine carcinomas are rare neoplasms accounting for about 5% of all tumors in this region. Like in the lungs, they encompass four entities: carcinoid, atypical carcinoid, small cell neuroendocrine carcinoma, and large cell neuroendocrine carcinoma [272]. For a detailed discussion of neuroendocrine neoplasms, the reader is referred to Chap. 11.

2.11.5.1 Carcinoid

Definition Sinonasal carcinoids are very rare well-differentiated neuroendocrine neoplasms that present bland cytology, lack of necrosis, and have <2 mitoses per 10 high-power fields [272].

Differential diagnosis, treatment, and prognosis are similar to carcinoids in other territories of the respiratory tract.

2.11.5.2 Atypical Carcinoid

Definition Sinonasal atypical carcinoids are moderately differentiated neuroendocrine carcinomas that present generally mild cytologic atypia, can have patchy necrosis, and have mitotic activity between 2 and 10 per high-power field. Although very rarely seen, a tumor with low mitotic activity, <2 per 10 high-power fields, that has bona fide necrosis is also considered atypical carcinoid [272].

Differential diagnosis, treatment, and prognosis are similar to those of atypical carcinoids in other territories of the respiratory tract.

2.11.5.3 Small Cell Neuroendocrine Carcinoma

Definition Small cell neuroendocrine carcinoma (SCNC) of the sinonasal tract is a high-grade, poorly differentiated, malignant epithelial tumor with histological features similar to small cell carcinoma of the lung [121].

Synonyms Small cell carcinoma, oat cell carcinoma, and poorly differentiated neuroendocrine carcinoma

Epidemiology This type of tumor 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, SCNC mainly arises from the ethmoid and maxillary sinuses and from the nasal cavity [273–277]. They may occur in pediatric age after treatment of retinoblastoma [278].

Etiology and pathogenesis Sinonasal SCNC is considered to derive from cells with neuroendocrine differentiation occasionally found in the seromucous glands.

Microscopy SCNC gives rise to nests, cords, and sheets of small undifferentiated cells, with molded nuclei and scanty cytoplasm (Fig. 2.52). More often than not, there is ulceration of the mucosa, but sometimes SCNC exclusively infiltrates beneath the surface epithelium. Foci of necrosis may be found and mitotic figures are frequently seen. Occasionally
the tumor grows surrounding the seromucous glands of the lamina propria, as if it was originating from them (Fig. 2.53). We have observed one case of SCNC originating at the base of a papillary NKSCC (Fig. 2.54). Variable degrees of neuroendocrine differentiation may be demonstrable by electron microscopy or immunohistochemistry (Fig. 2.55) [279]. Before placing a tumor within this category, a primary tumor from the lung must be ruled out.

**Immunohistochemistry** SCNC exhibits positive reaction for low molecular weight cytokeratins and EMA, as well as variable positivity for CD 56, synaptophysin, and chromogranin. At least two neuroendocrine markers should be positive [280].

**Differential diagnosis** Sinonasal SCNCs have been less precisely characterized than in other head and neck territories, and so far no unanimous consensus has been reached in regard to the way they have to be separated from other small cell tumors, either round or undifferentiated, occurring in this region [274–277, 281–284]. Table 2.5 provides the current criteria most widely accepted for their recognition. In addition, large cell neuroendocrine carcinoma has to be distinguished from SCNC [285, 286].

**Treatment and prognosis** Combination of surgery and radiotherapy, plus chemotherapy, is the treatment of
SCNC. Its prognosis seems to be somewhat better than for SNUC or for similar tumors of the lung.

### 2.11.5.4 Large Cell Neuroendocrine Carcinoma

**Definition** Large cell neuroendocrine carcinoma (LCNC) of the sinonasal tract is a high-grade, poorly differentiated, malignant epithelial tumor with histological features similar to its counterpart of the lung [272].

**Epidemiology** Only a few cases of LCNC have been reported in the sinonasal region [285, 286].

**Microscopy** LCNC is a tumor with high mitotic activity, but instead of having cells with high nuclear to cytoplasmic ratios, molding, and crush artifact, it has moderate to abundant cytoplasm.

**Differential diagnosis** Mitotic activity is the major histological feature that distinguishes LCNC from carcinoma and atypical carcinoma, >10 mitoses/10 HPFs in the former versus <10 mitoses/10 HPFs in the latter two.

**Treatment and prognosis** Surgery supplemented with postoperative radiotherapy and chemotherapy is the primary treatment for LCNC, which in general has the same poor prognosis as SCNC [272].

### 2.11.6 NUT Carcinoma

**Definition** NUT carcinoma is a rare, highly aggressive variant of poorly differentiated squamous cell carcinoma, which is defined by a rearrangement of the nuclear protein in testis (NUT) gene NUTM1 on chromosome 15q14 [287].

**Epidemiology** It is a rare tumor, but the exact incidence is unknown, because most cases have gone unrecognized due to the lack of specific diagnostic features. In two recently published studies, it represented 18% of poorly differentiated carcinomas of the upper aerodigestive tract [288] and 2% of sinonasal carcinomas [266].

**Clinical aspects** NUT carcinoma can occur at all ages, but patients with sinonasal involvement are mainly young adults. Presenting symptoms are nonspecific and include nasal mass and pain, proptosis, and toothache. The tumors involved in most cases both the nasal cavities and the paranasal sinuses [266, 288].

**Microscopy** Histologically, NUT carcinoma is composed of undifferentiated basaloid cells, with monotonous appearance, round to ovoid nuclei, and often clear cytoplasm. Areas of abrupt squamous differentiation can be present, in which mature keratinizing cells are juxtaposed to undifferentiated neoplastic cells. In some instances, squamous differentiation may be more pronounced [289]. Areas of necrosis and the presence of neutrophilic infiltrate are commonly observed. The surface epithelium may show areas of squamous metaplasia, but no evidence of dysplastic changes has so far been reported [266, 288].

**Immunohistochemistry** A monoclonal antibody to NUT for use in immunohistochemistry is currently available [290], which may help to separate NUT carcinoma from other poorly differentiated sinonasal carcinomas. This antibody is considered to be enough sensitive and specific, so that the demonstration of the NUTM1 rearrangement is no longer considered necessary [291]. Other immunohistochemical markers, which are consistently positive in NUT carcinoma, are cytokeratins, EMA, and p63, while no or limited immunoreactivity has been observed with muscle, neuroendocrine, and melanocytic markers. The presence of HPV and EBV infection has never been identified, either using immunohistochemistry, in situ hybridization, or polymerase chain reaction [292].

**Genetics** NUT carcinoma is characterized by a translocation involving the NUTM1 gene on chromosome 15q14 and, in most cases, the BRD4 gene on chromosome 19p13.1 [293]. The remaining cases either present a BRD3-NUTM1 fusion [t(9;15)(q34.2;q14)] or a yet uncharacterized fusion (so-called NUT-variant). The fusion gene encodes for a protein which is thought to be involved in a block of epithelial differentiation and squamous maturation [294].

**Differential diagnosis** It is difficult if not impossible to separate NUT carcinoma from other poorly differentiated carcinomas on pure morphological grounds. It has been suggested that some features that may support the inclusion of NUT carcinoma in the differential diagnosis are neoplastic cells with monotonous appearance, which vary in size from small to medium but are not large, and the presence of areas of focal “abrupt” keratinization [291]. The differential diagnosis in the sinonasal tract includes SNUC, poorly differentiated squamous cell carcinoma, basaloid squamous cell carcinoma, and neuroendocrine carcinoma. Among non-epithelial neoplasms, olfactory neuroblastoma, Ewing’s sarcoma, rhabdomyosarcoma (RMS), and hematolymphoid tumors can be considered in the differential diagnosis. The diagnosis of NUT carcinoma requires either the immunohistochemical demonstration of nuclear reactivity for NUT, which has a characteristic speckled pattern [290], or the demonstration of NUTM1 rearrangement by FISH or PCR. Other markers that may be useful in the differential diagnosis with the above-mentioned entities are p63, which is diffusely positive in NUT carcinoma, but not in SNUC and neuroendocrine carci-
noma, and neuroendocrine markers, which are not expressed or only focally expressed by NUT carcinoma.

**Treatment and prognosis**  NUT carcinoma has an extremely aggressive clinical course with short survival periods. According to a recent report, intensive local therapy, with complete surgical resection and radiation, seems to be associated with improved progression-free and overall survival. The type of translocation does not seem to affect prognosis [295].

### 2.11.7 SMARCB1–Deficient Sinonasal Basaloid Carcinoma

Recently, some tumors initially diagnosed as SNUCs as well as NKSCCs and myoepithelial carcinomas of the sinonasal tract have been shown to share a common alteration resulting in inactivation of the SMARCB1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1, also INI-1) tumor suppressor gene along with rhabdoid features, whether in isolated cells or in confluent sheets of polygonal cells with a plasmacytoid appearance. SMARCB1 deficiency can be easily identified through immunohistochemistry. Although the number of cases reported of these aggressive basaloid carcinomas is limited, it is likely that they represent a distinctive type of sinonasal carcinoma [296, 297].

### 2.11.8 Sinonasal Adenocarcinomas

Sinosal adenocarcinomas comprise a wide spectrum of glandular tumors accounting for approximately 20% of all sinonasal malignancies [298]. They show a remarkable wide range of histological appearances, and they arise both from mucosal seromucous glands and surface epithelium. The 2005 WHO classification recognizes three major adenocarcinoma subtypes: intestinal type, non-intestinal type, and salivary gland type.

#### 2.11.8.1 Intestinal-Type Adenocarcinoma

**Definition**  Intestinal-type adenocarcinoma (ITAC) is a tumor with histological features resembling colorectal dysplastic adenoma or adenocarcinoma [299, 300]. It is considered to originate through intestinal metaplasia of the ciliated respiratory cells lining the Schneiderian membrane. Metastasis from gastrointestinal adenocarcinoma should be ruled out before a tumor is labeled as a primary of this region.

**Epidemiology and etiology**  ITAC is the most common type of sinonasal adenocarcinoma representing about 6–13% of malignancies developing in the sinonasal tract [301–303]. It is strongly associated with exposure to different types of dust, mainly hardwood but also softwood dusts, as well as leather dust [304–310]. About 20% of sinonasal ITACs seem to be sporadic, without evidence of exposure to industrial dusts [298, 305]. The incidence has remained relatively stable in the last decades, although recently a decrease in the incidence of sinonasal adenocarcinomas has been observed in males [298, 311]. Males are more frequently affected than females, and the peak age is in the fifth and sixth decades, for both sexes. The most common location is the ethmoidal region [312], followed by the nasal cavities and other sinuses.

**Macroscopy**  ITACs have a fungating appearance with either polypoid or papillary features. Occasionally, they may have a gelatinous consistency resembling a mucocele. **Microscopy**  Histologically, ITAC is mainly composed of columnar mucin-secreting cells and of goblet cells [312]. Some well-differentiated tumors may also contain respiratory cells, argentaffin cells, and Paneth cells (Fig. 2.56). Endocrine-amphicrine enteric differentiation may occasionally be found [313]. Metaplastic and atypical changes have been observed in adjacent preneoplastic epithelium [314]. These tumors depict different histological patterns that may be predominantly (a) papillary, (b) glandular, (c) compact, (d) mucinous, and (e) mixed [312, 315]. Papillary tumors mainly consist of elongated outgrowths lined by intestinal-type cells with markedly atypical pseudstratified nuclei (Fig. 2.57). Although most of them are high-grade tumors, low-grade forms mimicking colonic villous adenoma may occasionally occur (Fig. 2.58) [316]. The glandular pattern resembles common-type intestinal adenocarcinoma (Fig. 2.59). 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 tumor is composed of dilated mucin-filled glands lined by columnar mucin-secreting epithelium and lakes of mucin containing fragmented epithelial elements (Fig. 2.60). Other mucinous tumors 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 behavior [317–319].

In rare instances, ITAC may be combined with small cell neuroendocrine carcinoma. In these cases, the two components are distinct and differ morphologically and immunohistochemically [320].

**Immunohistochemistry and electron microscopy**  Both technologies have confirmed the enteric differentiation of the tumor cells [321]. Wide-spectrum cytokeratin markers are positive, whereas CEA is only occasionally positive.
Cytokeratin 7 is frequently but not constantly positive, while most ITACs express cytokeratin 20 and CDX2, two markers related to intestinal differentiation [323]. Villin is another marker of enteric differentiation which is positive in these tumors [280]. Neuroendocrine markers, including chromogranin and synaptophysin, are frequently detected in individual cells or small clusters of cells, representing interspersed neuroendocrine or amphicrine cells [322, 324].

**Genetics**

The genotypic features of ITAC show a significant overlap with those present in colorectal adenocarcinoma, particularly with colorectal adenocarcinomas developing through the MSI-negative pathway [325]. Commonly altered genes include TP53, CDKN2A, and deleted in colon cancer (DCC), while, at variance with colorectal adenocarcinoma, the APC-beta-catenin pathway is likely to have a marginal involvement in the development of ITAC. In addition, activating KRAS mutations occur at a lower frequency (10–13%) than in colorectal cancer [326, 327]. The epidermal growth factor receptor (EGFR) is overexpressed in approximately 15% of ITACs, and most of these cases show either chromosome 7 polysomy or EGFR gene amplification by FISH analysis [328]. Conversely, activating mutations of EGFR and BRAF genes are rare or absent.

**Differential diagnosis**

ITAC can be differentiated from other adenocarcinomas on the basis of histological morphology and with the help of immunohistochemical markers of intestinal differentiation. These markers are characteristically expressed by ITACs but not by sinonasal non-intestinal-type adenocarcinomas.
Features such as cytologic atypia, high mitotic rate, and areas of necrosis, which are common findings in most ITACs, help to distinguish the high-grade variants from rare low-grade ITACs and from mucoceles. The lack of epidermoid and squamous differentiation separates these tumors from mucoepidermoid and adenosquamous carcinomas.

In rare occasions, adenocarcinomas originating in the gastrointestinal tract may metastasize to the sinonasal region, and this is usually a late event in the clinical course of the tumor. In these cases, the differential diagnosis with primary ITAC is mainly based on the clinical history, because no histological or immunohistochemical feature is distinctive enough to allow separation.

Treatment and prognosis Treatment of choice is complete surgical resection followed by radiotherapy. A good response to chemotherapy has been observed in some cases. Interestingly, chemotherapy was highly effective in tumors bearing wild-type or a still-efficient p53 protein, but ineffective in those carrying a disabled p53 protein, indicating that p53 status represents a promising predictive biomarker to chemotherapy in ITAC [329]. Prognosis of ITAC is generally poor and largely depends on T stage. Recurrences and subsequent deeply invasive local growth are frequent; however, lymph node and distant metastases are rare [310, 312, 318].

2.11.8.2 Non-intestinal-Type Adenocarcinomas

Sinonasal non-intestinal-type adenocarcinomas (non-ITAC) are an uncommon and heterogeneous group of tumors defined, by exclusion, as glandular malignancies that do not show signs of intestinal differentiation and do not resemble any salivary gland tumor type. Possibility of a metastatic adenocarcinoma should also be ruled out. They can be further distinguished in high- and low-grade subtypes.

High-Grade Non-intestinal-Type Adenocarcinomas

Definition High-grade non-ITACs are characterized by neoplastic non-intestinal and non-salivary type of glands showing moderate to marked cell pleomorphism, high number of mitotic figures, and foci of necrosis.

Epidemiology High-grade non-ITACs are rare tumors that develop more commonly in men, and, although they occur over a wide age range, they are much more common in older individuals [330].

Macroscopy They arise more often in the nasal cavity and maxillary sinus and appear as large destructive tumor masses, with areas of necrosis and hemorrhage.

Microscopy High-grade non-ITACs appear as poorly differentiated tumors, with predominantly solid growth pattern, and poorly formed gland structures. They show a great deal of heterogeneity, and different patterns have been recognized. The blastomatous pattern resembles primitive gland differentiation seen in teratocarcinosarcoma, with ribbons and trabeculae of neoplastic cells with numerous rosette-like gland structures sometimes containing mucus. In the apocrine subtype, the infiltrating glands resemble those of ductal carcinoma of the breast or high-grade salivary duct carcinoma. The oncocytic/mucinous can be associated with oncocytic Schneiderian papilloma and is formed by oncocytic and mucinous cells, growing as solid sheets and sometimes showing extracellular mucus accumulation [330]. The poorly differentiated/undifferentiated adenocarcinomas are predominantly solid with occasional cribriform nests and papillary structures.

Immunohistochemistry These tumors are consistently positive for cytokeratin cocktails and cytokeratin 7, while cytokeratin 20 and CDX2 are negative. Occasional cases have shown focal positivity for synaptophysin, S-100 protein, and p63.

Differential diagnosis High-grade non-ITAC can be distinguished from low-grade non-ITAC for the presence of prominent cytologic atypia, brisk mitotic activity, and/or necrosis. ITAC can be ruled out based on the lack of morphological resemblance to colorectal adenocarcinoma and for the absence of positivity to intestinal markers, such as cytokeratin 20, CDX2, and villin. Other poorly differentiated high-grade neoplasms to be considered in the differential diagnosis include salivary duct carcinoma and teratocarcinosarcoma.
Treatment and prognosis Although definitive specific treatment recommendations are lacking due to the rarity of this type of tumors, complete surgical excision is the treatment of choice, which may be followed by radiotherapy [331]. The prognosis, however, remains poor, with most patients experiencing local recurrence and death from disease.

Low-Grade Non-intestinal-Type Adenocarcinomas
Definition Low-grade non-intestinal-type adenocarcinomas (low-grade non-ITACs) are characterized by neoplastic non-intestinal and non-salivary type of glands showing absence or minimal cell pleomorphism, absence or minimal number of mitotic figures, and absence of necrosis.

Epidemiology Low-grade non-ITACs occur over a wide age range, with a mean of 60 years. There is no significant gender predilection. No relation with occupational activities has been documented in these tumors. The nasal cavity is the most commonly affected site, followed by the ethmoid sinus.

Macroscopy Given their rarity, precise data are not available.

Microscopy Different histological patterns may be recognized: papillary, tubular, tubulopapillary, glandular, mucinous, trabecular, cribriform, psammomatous, and clear cell. The papillary pattern is characterized by complex papillary fronds lined by bland columnar cells (Fig. 2.61). They may occasionally mimic oncocytic (columnar) cell papilloma. Recognition of invasion may be difficult in these cases. Quite similar tumors also develop in the nasopharynx [332]. The tubulopapillary carcinoma consists of a proliferation of cuboidal to columnar of epithelial cells, forming tubules at the center and papillae at the surface [333]; it has to be differentiated from the terminal tubulus adenocarcinoma of the nasal seromucous glands (Fig. 2.62) [334]. Tumors with glandular pattern may simulate adenoma; nevertheless, the presence of closely packed glands, forming back-to-back arrangements, indicates the true malignant nature of the lesion [335]. Papillary structures may be occasionally noted within dilated glandular structures. In a recent report, one-third of the cases were associated with respiratory epithelial adenomatoid hamartoma, but the significance of this finding is yet to be determined [336]. The clear cell pattern is best exemplified by the nasal renal cell-like adenocarcinoma, which consists of cuboidal to polyhedral adenocarcinoma with abundant clear cytoplasmic, forming either solid or glandular patterns that mimic clear cell renal carcinoma [337].

Immunohistochemistry Neoplastic cells are positive for broad-spectrum cytokeratins and cytokeratin 7, but not for cytokeratin 20, CDX2, MUC2, or villin. S-100 protein can also be detected [336]; positivity for myoepithelial markers has been reported in a few cases [338].

Genetics There are only sporadic reports of genetic analysis in these tumors. TP53 gene was not mutated in two cases examined by Franchi et al. [338].

Differential diagnosis Low-grade non-ITACs have to be distinguished both from benign and malignant lesions (Table 2.6). The main differential diagnosis is with sinonasal seromucinous hamartoma. The lack of lobular architecture; presence of epithelial tufting and papillae, “back-to-back” glands, areas with cribriform or trabecular pattern; and invasion of normal structures support the diagnosis of low-grade non-ITAC [42]. Respiratory epithelial adenomatoid hamartoma is characterized by gland-like structures lined by ciliated respiratory-type epithelium that originate from the
Adenoid Cystic Carcinoma

Definition

Adenoid cystic carcinoma (AdCC) is a malignant small cell tumor composed of ductal epithelial cells surrounded by modified myoepithelial cells, giving rise to tubular, cribriform, and solid patterns.

Epidemiology

AdCC is the most common malignant salivary type of tumor of the upper respiratory tract and comprises 5–10% of all sinonasal malignancies [302, 346, 347]. AdCC is most common in the maxillary antrum, followed by the nasal cavity [348], although ethmoid, sphenoid, and frontal sinuses may also be involved [142, 349, 350]. Invasion of the skull base by an AdCC has been recently documented [351].

Macroscopy

AdCCs present as unencapsulated masses of white to gray color and variable size.

Microscopy

Sinonasal AdCC is identical to that arising at other head and neck sites (Fig. 2.63). Over 50% present a cribriform growth pattern and less often solid or tubular growths [352]. Perineural growth and bone invasion are frequently observed (Fig. 2.64). Rarely, sinonasal AdCC may arise in a preexisting pleomorphic adenoma [353]. Examples of so-called dedifferentiated AdCC have also been reported in the sinonasal region [354]. These tumors consist of a con-

Table 2.6  Differential features of selected glandular lesions of the sinonasal tract

| Lesion                                      | Clinical features                  | Salient histopathologic features                                                                 | Immunohistochemistry                          |
|---------------------------------------------|------------------------------------|--------------------------------------------------------------------------------------------------|------------------------------------------------|
| Respiratory epithelial adenomatoid hamartoma (REAH) | Polypoid lesion; posterior nasal septum, ethmoid sinus, nasopharynx; wide age range, male predominance | Back-to-back glands lined by ciliated columnar cells, periglandular hyalinization; occasional mucinous change of proliferating epithelium | CK7+, CK20−, CDX2−, p63+ in the basal compartment, S100− |
| Seromucous hamartoma                        | Polypoid lesion; posterior nasal septum, nasopharynx; wide age range, slight male predominance | Lobular growth of small serous glands, uncommon mucinous glands; areas resembling REAH occasionally seen | S100+, CK7+, CK20−, CDX2−, myoepithelial markers | |
conventional low-grade AdCC component, with tubular or cribriform architecture, which is clearly separated from a high-grade undifferentiated or poorly differentiated carcinoma component.

**Differential diagnosis** Sinonasal AdCC must be mainly distinguished from other salivary gland-type tumors which occur in this territory, particularly pleomorphic adenoma, polymorphous low-grade adenocarcinoma, epithelial-myoepithelial carcinoma, and basaloid squamous cell carcinoma with cribriform pattern.

**Treatment and prognosis** Wide surgical resection is the usual treatment, which may be followed by radiotherapy. AdCC follows a protracted but relentless course, which at the outset may be silent. The majority of patients present with locally advanced disease; lymph node and distant metastases are a rare late event. The overall 5-year survival is around 60%, but the 10–20-year survival is poorer [355]. Patients with cribriform pattern may have a longer survival than patients with solid-type tumors [352]. Spontaneous regression of an AdCC of the nasal cavity has been recently reported [356].

**Mucoepidermoid Carcinoma**

**Definition** Mucoepidermoid carcinoma (MEC) is a malignant glandular tumor characterized by mucous, intermediate, and epidermoid cells. They are subdivided in low- and high-grade categories.

**Epidemiology** Sinonasal MEC is rare, representing less than 1% of all sinonasal carcinomas [357, 358]. Patients are usually adult, and there is no gender predilection [359]. The majority of tumors arise in the nasal cavity, followed by the maxillary sinus.

**Microscopy** The diagnosis of sinonasal MEC requires the identification of mucous, squamous, and intermediate cells (Fig. 2.65). Infiltration of the mucosa and bone is usually identifiable. The presence of cystic spaces is a frequent feature, while necrosis and atypical mitotic figures are rarely seen. The majority of tumors are in the low-grade category [359] although high-grade MEC may be encountered in the sinonasal tract [360].

**Differential diagnosis** In the sinonasal tract, the differential diagnosis of MEC includes mainly squamous cell carcinoma and adenosquamous carcinoma. Non-intestinal-type adenocarcinomas with clear cells and/or mucous production should also be ruled out.
**Acinic Cell Carcinoma**

**Definition** Acinic cell carcinoma (ACC) is a low-grade malignant neoplasm composed of cells with serous acinar differentiation.

**Epidemiology** ACC is uncommon in the sinonasal tract, and only a small number of cases have been documented in the nasal cavity [341, 361–365] and in the maxillary sinuses [366–368]. Most of them are single case reports.

**Microscopy** ACC is composed of four cell types, acinar, vacuolated, clear, and nonspecific glandular. They may give rise to the following main patterns: solid, microcystic, papillary cystic, and follicular [369].

**Differential diagnosis** The main tumors to distinguish from ACC are oncocytoma (Figs. 2.66 and 2.67), all the clear cell salivary-type tumors that may arise in the sinonasal tract and metastatic renal cell carcinoma [345]. Although mammary analogue secretory carcinoma (MASC) should be considered another differential diagnosis in cases of non-parotid ACCs, the single potential ethmoidal case so far studied was negative for the ETV6-NTRK3 translocation, which excluded MASC, and showed PAS-diastase-resistant zymogen granules typical of ACC [370].

**Treatment and prognosis** Surgical resection alone gives in most cases excellent results.

**Epithelial-Myoepithelial Carcinoma**

**Definition** Epithelial-myoeplithelial carcinoma (EMC) is a low-grade malignant tumor composed of variable proportions of two cell types which typically form duct-like structures. There is an inner layer of duct lining cells and an outer layer of clear cells [339].

**Epidemiology** EMC is quite rare in the sinonasal tract. Cases have been reported to involve the nasal cavity and maxillary sinus [371–377].

**Microscopy** The inner layer of the duct-like structures consists of small dark-staining cuboidal cells. The outer clear cells stain strongly for glycogen and are also positive for p63, vimentin, and smooth muscle actin; the inner luminal ductal cells are positive for cytokeratin cocktails and also for CK 19. There is considerable variation in the proportion of duct lining cells and clear cells, and not uncommonly, the latter are the predominant feature, forming sheets or nests of clear cells rather than ductal structures. The tumor is cytologically bland and mitoses are rare. Perineural and vascular invasion may be present and recurrence and metastases may develop.

**Differential diagnosis** Main differential diagnoses of EMC are myoepithelioma, pleomorphic adenoma, myoepithelial carcinoma, and adenoid cystic carcinoma.

**Treatment and prognosis** Wide surgical resection and adjuvant radiotherapy currently achieve excellent results in patients with EMC.

**Other Salivary-Type Adenocarcinomas**

Carcinoma ex pleomorphic adenoma [142, 378], myoepithelial carcinoma [147, 379], polymorphous low-grade adenocarcinoma (Figs. 2.68, 2.69, and 2.70) [380], and basal cell adenocarcinoma [381] have been reported in the sinonasal tract.
tract. Two to 10% of salivary duct carcinomas (SDCs) arise from the seromucous glands of the upper respiratory tract [382]. We have seen one example of SDC originating in the maxillary sinus, in which the characteristic ductal pattern, with comedo type of necrosis, was only evident in the metastasis to the submandibular lymph nodes. The primary tumor was initially classified as adenocarcinoma NOS (Figs. 2.71 and 2.72).

2.11.9 Primary Malignant Mucosal Melanoma

**Definition** Primary malignant mucosal melanoma (PMMM) of the sinonasal tract is a neoplasm derived from the melanocytes in the Schneiderian mucosa [383–385].
**Epidemiology** The head and neck region is the most commonly involved site in which PMMMs develop, being the sino-nasal tract its most frequent location [386, 387]. Sinonasal PMMMs account for less than 1% of all melanomas and for less than 5% of all sinonasal malignancies [386–389]. Although most series report a similar gender distribution, others indicate a slightly increased incidence in males [390, 391]. The tumors develop primarily between the fifth and eighth decades of life with a median age of presentation at approximately 60 years [391, 392]. They originate from melanocytes present in the mucosa of the respiratory tract (Fig. 2.73) [384, 385, 388]. In our experience, it is not uncommon to see melanoma arising in an area of squamous metaplasia (Fig. 2.74). In contrast to Caucasian, black Africans often show visible pigmentation at sites corresponding with the common locations of intranasal melanomas, for which they have a higher incidence [393].

**Clinical aspects** The signs and symptoms of presentation of sinonasal PMMMs are not specific. Epistaxis and nasal obstruction are frequent when located in the nasal cavity. PMMMs of the head and neck occur most frequently in the nasal cavity, where the lateral nasal wall and nasal septum are the most common sites of origin of the sinonasal tract. Melanomas arising from the lateral nasal wall account for almost half of the total. Middle and inferior turbinates and nasal vestibule are other possible sites. The maxillary sinus is the most commonly affected paranasal cavity, followed by the ethmoid, frontal, and sphenoid sinuses. Concurrent nasal and paranasal lesions are infrequent. The sinonasal PMMMs are usually advanced at presentation and the precise site of origin may be difficult to localize. Sinonasal PMMMs metastasize less frequently to lymph nodes but more frequently to the lungs and brain [390, 391, 394].

**Etiology** Unlike cutaneous melanomas, sinonasal PMMMs are not clearly related to ultraviolet radiation. Inhaled and ingested carcinogens, particularly products of smoking and formaldehyde, have been implicated in the pathogenesis, similar to other malignancies of the nasal cavity [395, 396].
**Genetics** An increased frequency of c-KIT (CD117) aberrations has been observed in PMMMs, while this is not the case in cutaneous melanomas [397]. Conversely, **BRAF** mutations that are increased in cutaneous melanomas are uncommon in PMMMs [398, 399]. Recently, it has been reported that in sinonasal PMMMs **NRAS** mutations and **CCDN1** amplification are more frequent than **KIT** or **BRAF** mutations [398]. Loss of p16 expression, **CDKN2A** mutations, and loss of heterozygosity are observed in up to 50% of PMMMs [400, 401].

**Macroscopy** Sinonasal malignant melanomas are either pigmented (black-brown) or nonpigmented (pink-tan) lesions. In the nasal cavity, they commonly arise in the anterior portion of the septum and present as tan-brown polypoid formations, with occasional ulcerated and hemorrhagic areas (Fig. 2.75). When arising within sinuses, they present as extensive and widely infiltrative tumors. The development of intranasal malignant melanoma in inverted papilloma has been reported [402].

**Microscopy** 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 labeled as primary tumors. Primary melanomas may be recognized by the presence of junctional activity or by the finding of an intraepithelial component in the adjacent mucosa; nevertheless, these features are usually lost in sinonasal mucosa because of the thinness of the surface epithelium and frequent ulceration in advanced stages of the disease. Melanomas are composed of medium- to large-sized cells that may be polyhedral, round, fusiform, 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 the various sinonasal salivary gland-type clear cell tumors. Osteocartilaginous differentiation has also been observed [403]. The cells of sinonasal melanoma grow in either solid, loosely cohesive, storiform, pseudo-alveolar, or organoid patterns [388]. Two-thirds of sinonasal melanomas contain some intracytoplasmatic brown pigment [388], which has to be confirmed as melanin (Fig. 2.76). In the sinonasal tract, nonpigmented melanomas are not uncommon; in our series in Barcelona, up to 40% of the sinonasal melanomas are amelanotic (Fig. 2.77). When melanin is scarce or is not found, diagnosis may be difficult, and special techniques are mandatory. Electron microscopy reveals the presence of premelanosomes and/or melanosomes (Fig. 2.78).

**Immunohistochemistry** The cells of melanotic and amelanotic malignant melanomas are negative for cytokeratin and positive for vimentin, S-100 protein, Melan-A, HMB-45, tyrosinase, microphthalmia-associated transcription factor...
Differential diagnosis The recognition of amelanotic malignant melanoma of the sinonasal tract requires ruling out a large list of entities. Epithelioid melanomas have to be mainly distinguished from non-keratinizing squamous cell carcinoma, but also from clear cell carcinomas as well as from epithelioid malignant schwannoma [410] and from metastatic renal cell carcinoma. Microcytic melanoma may mimic SNUC and other small round cell tumors (Table 2.5). Spindle cell melanoma may be mistaken for a variety of spindle cell sarcomas.

Treatment and prognosis The mainstay of treatment is radical surgical resection. Adjuvant radiotherapy seems to improve locoregional control but does not improve overall survival. Systemic therapy should be considered only for patients with metastatic or unresectable locoregional disease [394]. Patients with primary nasal melanomas had significantly better 5-year survival than do patients with melanomas from other head and neck sites [411]. 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, invasion deeper than 0.5 mm is associated with decreased survival [388].

Although many of the patients do not show initial lymph node involvement or disseminated metastases [388, 412, 413] and have stage I disease at the time of initial diagnosis, the prognosis is bad due to high recurrence rate [389]. This recurrence appears to be related to multicentricity of the tumors and to the anatomic characteristics of the region that preclude adequate resection, which is the treatment of choice [414, 415]. Patients with lower Ki-67 scores showed better survival than those with higher Ki-67 scores [416]. The utility of radiotherapy is controversial but it can be of use in unresectable cases or to control recurrences [415, 417]. Immunotherapy and chemotherapy are also used for metastatic disease [414]. Five-year survival of sinonasal PMMM ranges reportedly between 17 and 47% [389, 394, 414, 415, 418]. In our series in Barcelona, the 5-year survival is of 35%, which is similar to that of sinonasal SCC.

2.11.10 Olfactory Neuroblastoma

Definition Olfactory neuroblastoma (ONB) is a malignant tumor unique to the nasal cavity composed of neuroblasts derived from the olfactory mucosa that share neuroepithelial and neuroendocrine features [419–422].

Synonyms Esthesioneuroepithelioma, esthesioneurocytoma, and esthesioneuroblastoma

Epidemiology ONB is an uncommon malignant tumor representing about 2–3% of all sinonasal neoplasms [383]. ONB can affect patients of all ages and both sexes are equally involved [423]. Although a bimodal age presenta-
tion has been previously suggested, recent reports show an even incidence across all ages with peaks in the fifth and sixth decades [272]. This is clearly different from adrenal neuroblastoma, with most cases arising in children under 4 years of age.

**Clinical aspects** Nasal obstruction, rhinorrhea, and epistaxis are the most common presenting symptoms. The site of origin of ONB is confined to the olfactory mucosa that lines the upper part of the nasal cavity [424]. Occasionally ONB involves predominantly the superior aspect of the cribriform plate and grows as an intracranial tumor [425, 426]. Ectopic foci of the olfactory mucosa, the Jacobson’s or vomeronasal organ, sphenopalatine ganglion, ganglion of loci, and autonomic ganglia of the nasal mucosa are very rare potential sites of origin of ONB [427]. Before establishing a diagnosis of “ectopic” ONB, an extremely rare entity that implies absence of involvement of the olfactory membrane, other sinonasal small round cell tumors have to be carefully ruled out (Table 2.5).

**Genetics** ONB is characterized by a marked genomic instability with frequent chromosomal losses and gains [428]. ONB lacks the t(11;22) translocation characteristic of PNET [429]. It also lacks the molecular genetic changes of adrenal neuroblastoma, which, in children, may metastasize to the sinonasal region.

**Macroscopy** ONBs are often unilateral, presenting as smooth polypoid or fungating masses of fleshy consistency and yellow to pink color (Fig. 2.79).

**Microscopy** ONBs exhibit one of two main patterns of growth that bear diagnostic and prognostic implications [344]. This pattern approach is a valuable complement of the initial scheme proposed by Hyams et al. [114] to grade ONB in four groups (Table 2.7). The low-grade pattern comprises grades I–II of Hyams and the high-grade pattern grades III–IV. The low-grade pattern is seen most often, and it presents lobular arrangements with well-defined groups of tumor cells separated by abundant edematous and variably vascularized stroma (Fig. 2.80). Prominent vascularization may cause bleeding at the time of biopsy. The neoplastic neuroblasts are typically small, showing round to oval nuclei with stippled chromatin, absent or small nucleoli, and minimal cytoplasm; occasionally clear cell type cytoplasms may be found. Neuroblasts are commonly separated by a neurofibrillary matrix formed by neuronal cell processes, in which axons may be demonstrable (Fig. 2.81). This background, seen in about 85% of ONB, is the most helpful diagnostic feature. Homer Wright pseudorosettes are quite characteristic of ONB; however, they are less commonly seen. They form when the tumor cells surround the neurofibrillary matrix in collar-like arrangements. Perivascular pseudorosettes, formed by tumor cells arranged around capillaries, are of no diagnostic value, for they may be found in several types of neoplasms.
Less frequently seen is the high-grade pattern of ONB, in which the tumor grows as diffuse sheets of cells with presence of foci of necrosis and scanty but highly vascular stroma (Fig. 2.82). True olfactory Flexner-Wintersteiner rosettes are only seen in grade III ONBs; this uncommon type of rosettes depicts 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. Grade IV ONBs are anaplastic tumors and usually show pleomorphic nuclei, prominent eosinophilic nucleoli, increased mitotic rate, and conspicuous necrosis [427]. Very rarely, ONB may exhibit melanocytic or rhabdomyoblastic differentiation [430–432]. Exceptional examples of mixed ONB and carcinoma have also been reported [433].

Immunohistochemistry and electron microscopy ONB shows diffuse positivity for synaptophysin, CD56, and NSE (Fig. 2.83). Chromogranin is less often positive. In tumors with a nesting pattern, S-100 protein is positive in the peripheral sustentacular cells. Cytokeratin is generally negative, although in ONB with nesting pattern, a few tumors may exhibit focal staining for low molecular weight CKs. EMA is negative. Neurofilament protein and other markers of neural
Differentiation are more often expressed in tumors with diffuse, sheetlike pattern [421, 434–436]. Electron microscopy shows evidence of neuroblastic differentiation, demonstrating neuritic processes, neurotubules, and membrane-bound dense-core granules (Fig. 2.84) [437–439]. The human analogue of achaete-scute gene HASH1, expressed in immature olfactory neurons, is also expressed in olfactory neuroblastoma [440]. Conversely the olfactory marker protein [441], expressed exclusively in mature olfactory neurons, is not. ONB lacks CD 99 (MIC-2) expression [429, 442]. In a recent study, intense expression of olfactory-specific sensory transduction proteins was found in ONB, indicating that ONB and olfactory sensory neurons share the same lineage and that the detected transduction proteins could serve as specific tumor markers [443].

**Differential diagnosis** ONB must be distinguished from a wide variety of small round cell tumors arising in the sinonasal region (Table 2.5). While the diagnosis of low-grade ONBs is usually straightforward, particular care has to be taken before diagnosing high-grade ONBs, as glands of sinonasal non-intestinal-type adenocarcinomas should not be mistaken for the Flexner-Wintersteiner rosettes of ONB grade III; likewise the diffuse sheets of cells seen in either sinonasal undifferentiated carcinoma or in small cell neuroendocrine carcinoma may mimic grade IV ONB. Furthermore, ONBs with rhabdomyoblastic differentiation or mixed with carcinoma have to be differentiated from teratocarcinoma and those with melanocytic differentiation from malignant mucosal melanoma [444].

**Treatment and prognosis** Complete surgical excision with cribriform plate resection, often followed by radiation therapy and/or chemotherapy, seems to be the treatment of choice [419, 445, 446]. In advanced ONB, high-dose chemotherapy and autologous bone marrow transplantation have been used [447, 448]. Staging of ONB is based on the Kadish system [449], in which stage A disease is confined to the nasal cavity, stage B is confined to the nasal cavity and paranasal sinuses, and stage C shows local or distant spread beyond the nasal cavity or sinuses; most tumors present in stage C. This correlates with survival, which is about 90% for stage A, 70% for stage B, and 40% for stage C [449]. Recognizing the poor prognostic implications of regional and distant metastatic disease, adding cervical lymphadenopathy and distant metastasis as a fourth, stage D category was suggested [445], which showed a worse disease-free survival specifically for the D category [450] (Table 2.8).

**Necrosis** is the single histological feature that seems to correlate with poor survival [420]. 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 metastases account for the rest [423, 451]. Distant metastases mainly involve the bone and lung [448].

### 2.11.11 Ewing’s Sarcoma/Primitive Neuroectodermal Tumor (EWS/PNET)

**Definition** An exceedingly rare sinonasal tumor composed of poorly differentiated small round cells that shows varying degrees of neuroectodermal differentiation and originates from a pluripotential neuroectodermal cell progenitor [452, 453].

**Epidemiology** Approximately 9% of extraosseous EWS/PNETs arise in the head and neck region [279], and about 20% of them develop in the sinonasal tract, being the most common site the maxillary sinus, followed by the nasal cavity (Fig. 2.85) [453–455].
Etiology  EWS/PNET has been reported following radiotherapy for retinoblastoma [456–458].

Macroscopy  Sinonasal EWS/PNET may present as a soft polypoid mass.

Microscopy  EWS/PNET is composed of uniform, small, undifferentiated, primitive neuroectodermal cells (Fig. 2.86) [459]. Unusually, pseudorosettes and true rosettes may be found in these tumors.

Electron microscopy  EWS/PNET displays rudimentary neuritic differentiation, as well as scanty microtubule formation; dense-core granules are much less abundant than in olfactory neuroblastoma (Fig. 2.87).

Immunohistochemistry  The great majority of EWS/PNET will react strongly with antibodies against CD99 (Fig. 2.88). 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 [442].

**Genetics** The standard translocation t(11; 22) (q24; q12) of PNET [460] results in the fusion of the EWS-FLI1 genes. The detection of the chimeric transcript by techniques of molecular biology confirms the diagnosis [461–463].

**Differential diagnosis** Olfactory neuroblastoma, sinonasal undifferentiated carcinoma, lymphoma, rhabdomyosarcoma, and primary malignant mucosal melanoma are the main entities to rule out [262]. We have seen one example of EWS/PNET arising from the maxillary antrum, which ultrastructurally showed rudimentary neuritic differentiation, as well as scanty microtubule formation. This raised the differential diagnostic dilemma of “ectopic olfactory neuroblastoma”; nevertheless, the tumor cells were CD99 positive and showed the t(11;22)(q24;q12) translocation, findings that are characteristically negative in ONB [429].

**Treatment and prognosis** Multimodal therapy, which includes chemotherapy, radiotherapy, and surgery, offers the best results. Head and neck EWS/PNET has better prognosis than tumors of other sites. The overall 5-year survival rates reach between 60 and 70% [453].

### 2.11.12 Malignant Lymphomas

**Definition** Malignant lymphomas are small round cell tumors with phenotypic features of B/T cells and variable differentiation.

**Epidemiology** Sinonasal malignant lymphomas (SNML) account for approximately 13% of all upper aerodigestive tract lymphomas [205] and for 6% of all sinonasal malignancies [464]. In our own series, they account for 9.5% (Table 2.3). In western countries, about 50% of SNML are of B-cell-type and the other 50% mostly shows NK-/T-cell lineage [465], whereas other reports point to more variable rates [466–469]. Differently, in oriental populations, most primary lymphomas of the nasal cavity and nasopharynx are of NK-/T-cell lineage [470–473].

**Microscopy** Sinonasal B-cell lymphomas are in general composed of a diffuse proliferation of large lymphoid cells or of a diffuse mixed pattern of small and large cells (Fig. 2.89). 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. EBV markers are often negative. Sinonasal NK-/T-cell lymphomas were labeled in the past decades with terms such as “lethal midline granuloma,” “polymorphic reticulosis,” and angiocentric T-cell lymphoma, among others. Patients may present either with an obstructive mass or with midfacial destructive lesions. Histologically, an angiocentric and angiodestructive infiltrate with extensive necrosis and epitheliotropism is frequently seen. In extranodal NK-/T-cell lymphoma, cells may be small, medium sized, large, or anaplastic and may show a conspicuous admixture of inflammatory cells (Fig. 2.90). Pseudoepitheliomatous hyperplasia of the covering epithelium may occur, and when exaggerated, it should not be confused with squamous cell carcinoma [471]. Extranasal NK-/T-cell lymphoma is almost always associated with EBV positivity. The most typical immunophenotype is CD2+, CD56+, surface CD3−, and cytoplasmic CD3ε+. Most cases
are also positive for cytotoxic granule associated proteins (granzyme B, TIA-1, and perforin). Other T- and NK-cell-associated markers are usually negative. Sinonasal lymphomas demonstrating CD3ε+, CD56−, cytotoxic molecule+, and EBV+ are also included within the NK/T category. No specific cytogenetic abnormalities have been identified [474].

Differential diagnosis
SNML of either B-cell or T-cell derivation needs a careful distinction of other small round cell tumors (Table 2.5) and with extramedullary plasmacytoma [475, 476], as well as with extramedullary tumors composed of myeloid or lymphoid blasts [477].

Treatment and prognosis
Radiotherapy and chemotherapy CHOP regime has been the standard treatment for advanced sinonasal diffuse large B-cell lymphomas [478]. The addition of the anti-CD20 monoclonal antibody Rituximab® has led to a marked improvement in survival [479].

The treatment and prognosis of nasal NK-/T-cell lymphoma are variable. Initial treatment with radiotherapy alone or combined with multiagent chemotherapy is used. Some patients respond well to therapy and others die of disease despite aggressive therapy [472]. In recent years, the survival has improved with more intensive therapy [480]. For a detailed discussion of lymphoid lesions, the reader is referred to Chap. 13.

2.11.13 Extraosseous Plasmacytoma

Definition
A mass-forming lesion of monoclonal plasma cells that occurs outside the bone and bone marrow, without evidence of underlying multiple myeloma [481].

Epidemiology
More than 80% of extraosseous plasmacytomas develop in the head and neck region, and 44% of them involve the sinonasal region [482].

Clinical aspects
Full examination of the patient is required to exclude disseminated disease.

Microscopy
Plasmacytoma of the sinonasal tract usually appears as a diffuse infiltration of mature plasma cells of the mucosa; occasionally, tumor cells are less differentiated, and diagnosis may be difficult exclusively on histologic basis [475, 476, 483, 484].

Immunohistochemistry
Staining for CD138 and κ and λ chains may be helpful. CD19 is nearly always negative and CD56 and CD117 are often aberrantly expressed.

Differential diagnosis
Mucosal lymphomas with plasmacytic differentiation, particularly extranodal marginal zone (MALT) lymphoma, may be misinterpreted as extramedullary plasmacytoma.

Treatment and prognosis
Most extraosseous plasmacytomas are cured with local radiation therapy. Regional recurrences occur in one-fourth of patients; distant extraosseous metastasis may occasionally occur [482].

2.11.14 Malignant Soft Tissue Tumors

Malignant soft tissues tumors of the sinonasal tract are very rare neoplasms and account for about 5% of all the malignancies in this territory (Table 2.3). Only the most salient of these entities are covered here. For a detailed discussion of soft tissue tumors, the reader is referred to Chap. 12.

2.11.14.1 Fibrosarcoma

Definition
A malignant mesenchymal tumor composed of fibroblast with variable collagen production and in prototypical cases a herringbone pattern [485].

Synonym
Adult fibrosarcoma.

Epidemiology
Most of head and neck fibrosarcomas occur in the sinonasal tract and are seen across a wide age range [486–489]. They are considered the second most common soft tissue sarcoma after rhabdomyosarcoma in the head and neck [490].

Clinical aspects
Fibrosarcomas most commonly cause obstruction and epistaxis [163]. An ethmoid sinus fibrosarcoma arising as a frontal sinus mucocele has been reported [491].
Microscopy  The histological 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 low mitotic rate [492]. In accordance, the behavior is more often characterized by repeated local recurrences, while distant metastases are rare.

Differential diagnosis  It includes desmoid-type fibromatosis, leiomyosarcoma, nerve sheath tumors, spindle cell carcinoma, and desmoplastic melanoma.

Treatment and prognosis  Surgery is the recommended treatment, often followed by radiotherapy [490].

2.11.14.2 Undifferentiated Pleomorphic Sarcoma

Definition  The name undifferentiated pleomorphic sarcoma (UPS) has nowadays replaced the until recently used term malignant fibrous histiocytoma (MFH), which was commonly employed as a diagnosis of exclusion for sarcomas mainly composed of myofibroblasts or undifferentiated mesenchymal cells [490].

Epidemiology  A considerably decrease in the frequency of the diagnosis of MFH has occurred following the advent of immunohistochemistry. About 3% of MFH develop in the head and neck, and 30% of these arise in the sinonasal region. They most often are seen in adulthood [490].

Etiology  MFH represents the most common post-radiation sarcoma, although they are predominantly sporadic.

Microscopy  MFH is a high-grade sarcoma, histologically consisting of a proliferation of spindle cells arranged in 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 [166].

Differential diagnosis  Before a diagnosis of malignant fibrous histiocytoma is rendered, other pleomorphic malignant tumors, like leiomyosarcoma, osteosarcoma, and sarcomatoid carcinoma, should be excluded by means of immunohistochemical or ultrastructural analysis.

Treatment and prognosis  Complete surgical resection is the recommended treatment, often followed by radiotherapy. Prognosis is related to the extension of the tumor.

2.11.14.3 Leiomyosarcoma

Definition  Leiomyosarcoma (LMS) of the sinonasal tract is an extremely rare malignant neoplasm, with identical histological and immunophenotypic appearance to its soft tissue counterpart [166].

Epidemiology  Sinonasal LMS accounts for less than 1% of all soft tissue tumors in this region [490].

Microscopy  As in other territories, LMS is composed of right-angle intersecting bundles of spindle cells with eosinophilic cytoplasm and “cigar-shaped” nuclei. Foci of necrosis, increased mitotic activity, and cellular atypia are present.

Immunohistochemistry  Cells of LMS are reactive for smooth muscle and/or muscle-specific actin, desmin, h-caldesmon, and vimentin.

Differential diagnosis  Sinonasal LMS must be distinguished from leiomyoma, glomangiopericytoma, and other spindle cell malignant tumors.

Treatment and prognosis  Sinonasal leiomyosarcoma can be regarded as a locally aggressive neoplasm with limited metastatic potential that should be treated by surgery alone if the tumor is limited to the nasal cavity [493]. Adjuvant radiochemotherapy may be used in advanced tumors.

2.11.14.4 Rhabdomyosarcoma

Definition  Rhabdomyosarcoma (RMS) is a malignant mesenchymal tumor of skeletal muscle phenotype [490].

Epidemiology  RMS is the most common sinonasal malignancy of the pediatric age, [494, 495]. The most common histologic subtypes are the embryonal and the alveolar [494]. RMS is predominantly seen in children and young adults, but they may also occur in older adults, specially the alveolar subtype [490].

Macroscopy  The botryoid variant of embryonal RMS has a characteristic grapelike or polypoid appearance, while the other subtypes/variants show an indistinct fish-flesh appearance.

Microscopy  Embryonal RMS is characterized by the presence of small, eosinophilic polygonal, or spindled cells with hyperchromatic nuclei and occasional cytoplasmic cross striations; the cell population is usually dense or intermingled with myxoid stroma. Alveolar RMS has fibrous septa, separating clusters of loosely cohesive small round cells with hyperchromatic nuclei and scant eosinophilic cytoplasm; the presence of multinucleated giant cells is a typical feature (Fig. 2.91). Other variants of RMS include sclerosing, spindled, botryoid, and pleomorphic forms [490, 496].

Immunohistochemistry  The diagnosis of RMS can be confirmed by immunostaining for myogenin and MyoD1,
which are nuclear markers with high specificity for skeletal muscle differentiation. Less specific are desmin, muscle-specific actin, and myoglobin.

**Genetics** Alveolar RMS typically harbors t(2;13) or t(1;13) translocations resulting in PAX3-FOXO1A or PAX7-FOXO1A gene fusions. Embryonal RMS harbors more complex genetic alterations, such as loss of the tumor suppressor CDKN2A, mutation/amplification of FGFR4, gain of GLI1, and mutations in the myogenic transcription factor MYOD1 [497–499].

**Differential diagnosis** It includes all sinonasal undifferentiated small round cell tumors. Furthermore, it must be kept in mind that rhabdomyoblastic differentiation may be encountered in tumors other than RMS [444]. This fact is important because RMS is treated by specific chemotherapy protocols that may be different than those of other tumors in the differential diagnosis.

**Treatment and prognosis** Treatment includes a combination of radiotherapy and chemotherapy, with surgical resection reserved for residual disease. The risk for neck involvement is high. With the advent of more aggressive therapy, the overall 5-year survival has increased from 40 to 70% [500]. Adult age and alveolar subtype are adverse prognostic factors in RMS.

### 2.11.15 Malignant Peripheral Nerve Sheath Tumors

**Definition** A malignant tumor of nerve sheath phenotype [490].

**Synonyms** Neurofibrosarcoma, malignant schwannoma, and neurogenic sarcoma

**Epidemiology** The head and neck is one of the more common anatomic areas to be affected by malignant peripheral nerve sheath tumors (MPNSTs) [501]. MPNST of the sinonasal tract is a very rare neoplasm [502]. Most arise de novo or less often in the context of neurofibromatosis type 1 (NF1) [503–505]. There is female predominance for the novo sinonasal MPNST [492] and male predominance in NF1-associated MPNST [490, 506].

**Etiology** Radiation and immunosuppression may be causative agents of MPNSTs [507].

**Microscopy** MPNSTs typically grow in a herringbone-type fascicular pattern. MPNST is a highly cellular spindle cell proliferation and exhibits nuclear hyperchromasia, pleomorphism, elevated mitotic rates, and necrosis. Typically, dark hypercellular areas alternate with light, less cellular ones, conferring a so-called “marbleized” appearance [501]. Sinonasal MPNSTs are often low grade, in contrast to those arising at other sites [492]. In poorly differentiated MPNSTs, the diagnosis can be based on the identification of a preexisting neurofibroma. The epithelioid variant of MPNST has been described in the sinonasal tract and may mimic amelanotic malignant melanoma (Fig. 2.92) [410]. Some tumors may show morphological and immunohistochemical features of skeletal muscle differentiation and are designated as “malignant Triton tumor” [492, 508]. The majority of malignant Triton tumors occur in the setting of NF1. About a third of malignant Triton tumors involve the head and neck [444].
Immunohistochemistry In MPNSTs the nerve sheath markers S100 and SOX10 are positive, but usually have focal distribution; in contrast, epithelioid MPNSTs stain diffusely for S-100.

Genetics Both NF1 alleles are inactivated in MPNSTs ex neurofibroma associated with NF1.

Differential diagnosis It includes fibrosarcoma, leiomyosarcoma, synovial sarcoma, spindle cell carcinoma, and malignant melanoma. Furthermore, positivity for S-100 in a spindle cell sarcoma as present in MPNST may also be shown by the recently described sinonasal biphenotypic sarcoma, a low grade sarcoma that shows immunohistochemically demonstrable neurogenic and myogenic differentiation [509].

Treatment and prognosis Surgical removal is the mainstay treatment that may be followed by radio- and chemotherapy.

2.11.16 Biphenotypic Sinonasal Sarcoma

A new entity known as low-grade, biphenotypic, sinonasal sarcoma has been recently recognized [509]. In addition to distinguishing histological and immunohistochemical features, this tumor is often hallmarked by a recurrent PAX3-MALM3 gene fusion [510]. It occurs in adults, predominantly women, being characterized by a submucosal proliferation of spindle cells with scant mitotic activity and concomitant neural and myogenic differentiation. Benign glandular proliferation is often present; the majority of glands are lined by respiratory type of epithelium, but areas of oncocytic and squamous metaplasia may be encountered. Hemangiopericytoma - like blood vessels are conspicuous. Focal rhabdomyoblastic differentiation may be seen. Bone invasion emphasizes the infiltrative nature of the lesion. Local recurrence rate approaches 45%, but no patient has developed metastases or died of disease.

2.12 Germ Cell Tumors

Teratoma is the principal benign germ cell tumor of the sinonasal region and shows histological features similar to its counterparts in the gonads and in other extragonadal locations. Malignant tumors with histological features similar to germ cell tumors of the gonads arise on rare occasions in the sinonasal tract. Immature teratomas and teratomas with malignant transformation are tumors of infancy and early childhood, whereas sinonasal endodermal sinus tumors and sinonasal teratocarcinosarcoma have only been documented in adults [511].

2.12.1 Dermoid Cyst

Definition A dermoid cyst is a developmental lesion histogenetically and histologically composed of ectoderm and mesoderm, but no endoderm [511].

Synonyms Nasal dermoid sinus cyst and cystic dermoid

Epidemiology Dermoid cysts of the nose comprise 3% of all dermoids and 5.5–12% of those of the head and neck region [512, 513]. A male predominance has been described for cystic dermoids. More than half are detected in children 6 years old or less, and approximately a third are present at birth [514]. Dermoid cysts of the head and neck are located more often in the subcutaneous tissue of the lateral suprabital ridge and nose. In the nose, they occur most commonly in the bridge and always in the midline. The glabella, nasal tip, and columella are less common sites [512–515]. A few cases have been described as originating in the paranasal sinuses [516].

Etiopathogenesis The most likely explanation for the ontogeny of dermoid cysts is the retention of ectodermal tissue along the lines of closure at junctions of bones, soft tissues, and embryonic membranes [515].

Clinical features Nasal dermoid cysts manifest as a midline nasal pit, fistula, or subcutaneous infected mass. They may cause broadening of the nasal bridge and occasionally cellulitis or purulent discharge. On palpation, the cysts are soft to fluctuant with a pale yellowish-pink color noted beneath the thinned but intact epithelium; when keratin debris and sebum fill the lumen, they may have a doughy consistency [512–515]. Most patients do not have other malformations, but 6–41% have associated congenital malformations [517, 518]. Computed tomography and magnetic resonance imaging scans are valuable in determining the intracranial and nasal components of a lesion and excluding encephalocele [512–516].

Macroscopy The cysts may range in size from a few millimeters to 12 cm in diameter. The lumen contains cheesy, yellow-white material.

Microscopy Dermoid cysts are lined with mature keratinizing squamous epithelium and frequently contain appendages of the skin in the cyst wall but no endoderm.

Differential diagnosis This lesion is differentiated from a teratoma by the limited variety of tissue types and the absence of endodermal components. Epidermal inclusion cysts may resemble cystic dermoids but do not contain adnexa. Epidermal inclusion cysts occur more frequently in...
adults, in contrast to dermoids, which are more commonly found in children and young adolescents [514–516]. Dermoid cysts should be clinically differentiated from encephalocele, which occurs in the same anatomic area.

**Treatment and prognosis** Dermoid cysts are treated by complete surgical excision, regardless of the extent of the lesion. The recurrence rate has been reported to be less than 7% [512–515].

### 2.12.2 Mature Teratoma

**Definition** Mature teratomas are tumors composed of a variety of mature tissues that are foreign to their sites of occurrence. There are typically tissues derived from two or three germ layers [511].

**Synonyms** Teratoid tumor, benign teratoma and mature cystic teratoma

**Epidemiology** Teratomas of the head and neck region account for only 6% of all teratomas [519, 520]. Mature teratomas in the sinonasal tract are even more unusual [521]. The majority of sinonasal teratomas occur in neonates and infants, and an equal sex distribution has been reported [521, 522]. Stillbirth, prematurity, fetal malpresentation, dystocia, and maternal polyhydramnios are frequent accompaniments. The orbit, oropharynx, and neck are classic locations for mature teratomas of the head and neck, but these tumors have been found rarely in the sinonasal tract [521]. In the sinonasal tract, the maxillary antrum and nasal cavity are affected more often than is the sphenoid sinus [519, 523–525].

**Etiopathogenesis** The exact origin of teratomas is not yet known, although numerous theories have been presented. The most popular theories of their origin are that they derive from primordial germ cells or from primitive somatic cells that escaped the influence of organizers and inducers [520].

**Clinical features** Manifestations of teratomas depend on the specific location of the tumors. Signs and symptoms usually result from compression of adjacent organs and tissues. Facial deformity, nasal obstruction, and a nasal mass are common manifestations of sinonasal teratomas. The occasional calcifications seen in computed tomography and magnetic resonance imaging scan provide the most valuable aids in resolving the differential diagnosis [519, 521, 524]. Teratomas may be associated with other skull deformities, anencephaly, hemicrania, and palatal fissures [519].

**Macroscopy** The tumors are usually cystic, but they can be solid or multilocular. They are commonly encapsulated masses that measure up to 7 cm at their largest dimension.

**Microscopy** Teratomas are composed of varied admixtures of mature skin, appendages of the skin, fat, glial tissue, smooth muscle, cartilage, bone, minor salivary glands, and respiratory and gastrointestinal epithelium. Neural tissues may be seen more often in sinonasal teratomas than in other teratomas.

**Differential diagnosis** Although the variegated histological appearance of mature teratomas is usually diagnostic, nasal glial heterotopia and meningocele should be considered in the differential diagnosis. The presence of immature elements or any other germ cell tumor excludes mature teratoma.

**Treatment and prognosis** Complete surgical excision has been curative in the few cases of sinonasal mature teratomas reported in the literature.

### 2.12.3 Immature Teratoma

**Definition** Immature teratomas are composed of variable quantities of immature tissue elements, mostly neuroepithelial, that appear interspersed with mature tissues derived from the three embryonic germ layers [511].

**Synonym** Teratoma with immature elements

**Epidemiology** Immature teratomas are tumors of infancy and childhood [121].

**Etiopathogenesis** The histogenesis of this type of tumor remains unsettled, as it is the case for mature teratomas. Either the displaced, persistent germ cell theory or the possibility of an alternative progenitor cell has been discussed [526].

**Clinical features** Symptoms are not specific. Nasal discharge and airway obstruction are common. Imaging procedures show expansive growth without invasive destruction.

**Macroscopy** In contrast to mature teratomas that are usually cystic, immature teratomas tend to be either solid-nodular or a combination of solid and cystic tumor masses; however, this is not a consistent observation.

**Microscopy** The distinction between mature and immature teratomas is based on their microscopic appearances.
The tumor may contain cystic spaces lined by mature ciliated pseudostratified epithelium and immature areas with primitive neuroepithelial rosettes lined with multilayered neuroblasts. Mitotic figures are frequently present in the immature arrangements; however, cellular atypia is not found.

**Differential diagnosis** In infants and children, a teratoma with malignant transformation has to be excluded. In adult patients, thorough sampling of the specimen is mandatory to rule out teratocarcinosarcoma.

**Treatment and prognosis** Complete surgical excision is usually an effective treatment. Despite the immaturity of its tissue elements and of the presence of mitotic figures, immature teratomas rarely behave in a malignant fashion [526].

### 2.12.4 Teratoma with Malignant Transformation

**Definition** Teratoma with malignant transformation is a neoplasm containing benign tissue elements of all three germinal layers and, in addition, a specific type of malignant tumor [511].

**Synonym** Malignant teratoma

**Epidemiology** In the head and neck, malignant transformation of a teratoma is a distinctly uncommon observation. Involvement of the sinonasal tract by such a lesion is extremely rare. Kuhn et al. reported of a case of squamous cell carcinoma arising in a benign teratoma of the maxilla of a 13-month-old boy [527]. Petrovich et al. reported a nasal malignant teratoma in a 63-year-old man [528].

**Clinical features** A fluctuating left facial swelling occurred during a period of 9 months prior to the diagnosis. On computed tomography scans, thickened left maxillary sinus mucoperiostium and a soft tissue defect were observed over the alveolar ridge. Metastatic disease was not found.

**Macroscopy** A soft tissue mass of 2.0-cm diameter in the left maxillary alveolar ridge with displacement of unerupted teeth has been noted [527].

**Microscopy** The tumor was composed of variable mature tissue elements of ectodermal, mesodermal, and endodermal derivation consistent with extragonadal teratoma. An additional finding was the presence of an atypical squamous proliferation with the features of squamous cell carcinoma [527].

**Differential diagnosis** It includes immature teratoma with pseudocarcinomatous proliferation of the squamous epithelium and odontogenic cyst.

**Treatment and prognosis** The tumor reported by Kuhn et al. was locally aggressive and recurred after surgery. There was no evidence of further recurrence 2 years after chemotherapy [527].

### Yolk Sac Tumor

**Definition** Yolk sac tumor (YST) of the sinonasal tract is a primary malignant neoplasm found to arise in this location that has histological features indistinguishable from yolk sac tumor of the gonads [511].

**Synonyms** Endodermal sinus tumor, yolk sac carcinoma, and orchioblastoma

**Epidemiology** Only 20% of YSTs are extragonadal [529]. Head and neck YSTs are very rare, and similarly to the gonadal counterpart, they have two distinct peaks of incidence; the most common one is seen in the early years of life and the less frequent in adult age [526, 529–533].

**Pathogenesis** The development of a germ cell malignancy does not need always to be explained by the neoplastic transformation of a primordial germ cell. Alternatively, YSTs of the adult may evolve from precursor somatic neoplastic cells by a process of divergent differentiation toward structures resembling the fetal yolk sac [534].

**Clinical aspects** While the YSTs that develop in infancy and childhood may be associated or not to a teratoma, those occurring in adult patients may associate or not to a somatic carcinoma [534–538]. The two sinonasal YSTs reported in adults developed in men aged 43 and 59 years [534, 537]. Both tumors occupied the paranasal sinuses with focal orbital and cranial destruction. YSTs are known to secrete alpha-fetoprotein (AFP). A case of sinonasal YST admixed with choriocarcinoma has been documented [535].

**Macroscopy** YSTs tend to be gray white to yellow, focally hemorrhagic.

**Microscopy** The most characteristic pattern of growth of YSTs is composed of pseudopapillary structures with numerous glomeruloid or perivascular Schiller-Duval bodies and labyrinthine cavities and channels lined by flattened to cuboidal epithelium with various degrees of atypia (Fig. 2.93). Another common pattern is the reticular or microcystic, in which eosinophilic hyaline globules, PAS
positive and diastase resistant, are found intracellularly and extracellularly. The solid pattern is composed of densely cellular nests and cords of immature elements that may differentiate into somatic endodermal derivatives (Fig. 2.94). Another pattern is the polyvesicular vitelline. Surrounding these tissue patterns, there are variable amounts of reactive stromal component.

**Immunohistochemistry** AFP is the characteristic marker of the pseudopapillary and reticular structures of YSTs. The solid pattern mainly immunoreacts with wide-spectrum cytokeratin cocktails and CK20. Beta-HCG is negative in pure YSTs, unless combined with choriocarcinoma [535].

**Differential diagnosis** Sinonasal YSTs must be distinguished from other germ cell tumors occurring in this region, mainly from teratocarcinosarcoma. The solid pattern of YSTs must be distinguished from somatic malignancies with undifferentiated carcinoma component and from basaloid non-keratinizing squamous cell carcinoma.

**Treatment and prognosis** Complete excision, whenever possible, followed with radiochemotherapy is the recommended treatment of YSTs. Owing to the aggressive behavior of these gonadal or extragonadal tumors in adult patients, platinum-based therapy should be added [533].

### 2.12.6 Teratocarcinosarcoma

**Definition** Sinonasal teratocarcinosarcoma (SNTCS) is a complex malignant sinonasal neoplasm combining features of teratoma and carcinosarcoma. Benign and malignant epithelial, mesenchymal, and neural elements are typically present, including immature tissue with blastomatous features [511, 539].

**Synonyms** Teratocarcinoma, teratoid carcinosarcoma, blastoma

**Epidemiology** SNTCS is very rare [540]. Patients are exclusively adults, with ages ranging from 18 to 79 years (mean 60 years) [539–544]. There is a marked male predominance. SNTCS almost exclusively arises in the ethmoid sinus and maxillary antrum, although it may arise in other head and neck territories [539, 545, 546].

**Etiology and pathogenesis** SNTCS is unlikely to be a germ cell tumor, but probably arises from pluripotent stem cells of the neuroepithelium that not only reproduce the neuroectodermal features of olfactory neuroblastoma but also have the capacity to differentiate into divergent types of somatic cells [543]. In contrast with malignant gonadal teratomas, which are frequently found in patients at younger age, SNTCS does not contain areas of embryonal carcinoma, choriocarcinoma, or seminoma as seen in many germ cell tumors [539].

**Clinical aspects** Patients present with a short history of nasal obstruction and epistaxis. Imaging studies reveal a nasal mass occasionally accompanied by opacification of the paranasal sinuses. Bone destruction may be seen [539].

**Macroscopy** Tumors are usually bulky, soft to rubbery, and red tan to purple. A mass filling the nose and projecting for about 3 cm from the naris has been documented [547].
Microscopy  SNTCS is made up of multiple tissue types derived from two or three germ layers, often forming cystic spaces and exhibiting variable degrees of maturity and undifferentiated/primitive component (Fig. 2.95). In addition there are carcinomatous and sarcomatous components [540, 544]. The epithelial component includes keratinizing and non-keratinizing squamous epithelium, pseudostratified columnar ciliated epithelium, and glandular structures lined by either cuboidal or columnar cells that may show mucous differentiation (Fig. 2.96). Nests of immature squamous cells containing clear cells which are “fetal appearing” are a common finding and an important diagnostic clue [539]. The carcinomatous component is usually glandular, but sometimes squamous. Neuroepithelial elements with rosettes and neuroblastoma-like areas are in most instances present (Fig. 2.97). These epithelial and neuroepithelial elements occur in close relationship with each other and with mesenchymal elements. The most prominent mesenchymal elements are immature cells with oval or elongated nuclei. The mesenchymal cells may exhibit skeletal muscle differentiation with cross striations and bizarre formations (Fig. 2.98). Foci of cartilage, smooth muscle, adipose tissue, and fibrovascular tissues may also be present. There may be proliferation of small round cells that are difficult to classify. Mitotic activity and cytological features of malignancy are demonstrable in the undifferentiated areas of both the epithelial and mesenchymal elements [540].

Immunohistochemistry  The undifferentiated/primitive component often shows positive immunoreaction for CD99 and occasionally for synaptophysin and S-100 protein [543]. The spindle cell component is consistently positive for vimentin and sometimes for desmin, myoglobin, and glial fibrillary acidic protein. The neuroepithelial component is positive for neuron-specific enolase and occasionally for chromogranin, alpha-fetoprotein, cytokeratin, and neurofilaments [540]. The epithelial component is positive for cytokeratins, epithelial membrane antigen, and occasionally S-100 protein and glial fibrillary acidic protein.

Differential diagnosis  Small biopsies and/or inadequate sampling of SNTCS specimens may lead to erroneous diagnoses of olfactory neuroblastoma, squamous cell carcinoma, undifferentiated carcinoma, adenocarcinoma, malignant salivary gland-type tumors, and adenosquamous carcinoma [539].

Treatment and prognosis  Aggressive initial therapy with a combination of surgical resection, radiotherapy, and chemotherapy is usually recommended [539]. SNTCSs are locally aggressive tumors, with rapid invasion of soft tissues and bone, and metastasize to regional lymph nodes and
sites, such as the lung. Craniospinal dissemination may occur [548]. The average survival of SNTCS is less than 2 years, with 60% of the patients not surviving beyond 3 years [539]. Improved outcomes have been reported in more recent years [546].

2.12.7 Choriocarcinoma

Definition Choriocarcinoma is a malignant neoplasm composed of syncytiotrophoblast, cytotrophoblast, and intermediate trophoblast [549].

Synonym Non-gestational choriocarcinoma

Epidemiology Sinonasal choriocarcinoma is an extremely rare entity. Of the two cases reported, one originated in the maxillary sinus, and the other affected the nasal cavity, ethmoid and sphenoid sinuses. Both patients were males, one 44 years of age and the other 49 year old [550]. Improved outcomes have been reported in more recent years [546].

Clinical features One patient presented with epistaxis and the other with nasal obstruction. Both had elevated beta-HCG in serum.

Macroscopy Tumors are soft and hemorrhagic.

Microscopy Tumors are composed of an admixture of small, round to polygonal cytotrophoblastic cells, forming fenestrated sheets or pseudopapillae, surrounded by large multinucleated syncytiotrophoblastic cells.

Immunohistochemistry All choriocarcinoma cells are positive for pancytokeratin and syncytiotrophoblast reacts with beta-HCG.

Differential diagnosis Before establishing a diagnosis of primary sinonasal choriocarcinoma, it is mandatory to rule out metastatic gestational or non-gestational disease [551, 552].

Treatment and prognosis Patients with primary sinonasal choriocarcinoma are tributary of the aggressive chemotherapy regimens for non-gestational choriocarcinoma. Gestational choriocarcinoma requires less aggressive therapy.

2.13 Metastatic Tumors

Definition Sinonasal metastatic tumors are secondary malignancies that derive from a noncontiguous neoplasm. Direct extension from an adjacent neoplasm and leukemia-lymphoma is excluded [553, 554].

Synonym Secondary tumors

Epidemiology Metastases to the nasal cavity and paranasal sinuses are rare [555, 556]. The median age of patients with sinonasal metastatic tumors is 57 years, range 3 months to 76 years, and about 60% occur in males [557]. The most frequent primary sites of origin of the tumors are the kidney (40%), lung (9%), breast (8%), thyroid (8%), prostate (7%), and miscellaneous (28%) [556]. The most habitual anatomic sites involved by the metastases are maxillary (33%), sphenoid (22%), ethmoid (14%), frontal (9%), and multiple sinuses (22%) [556, 558]. In 10–15% of cases, the metastases are limited to the nasal cavity [553].

Clinical aspects Metastases of tumors to the sinonasal tract are hematogenous and may be solitary or multifocal [554]. Usually symptoms are indistinguishable from those of a primary sinonasal tumor. Epistaxis is particularly common in metastatic renal and thyroid carcinomas; other common symptoms are nasal obstruction, headache, facial pain, visual disturbances, exophthalmos, facial swelling, and cranial nerve deficits. Metastases may be the first manifestation of an otherwise clinically occult carcinoma [553].

Microscopy Often, metastatic tumors to the sinonasal tract reproduce the most common histological features depicted by the primary tumors, which facilitates their recognition. Most renal cell carcinomas are of the clear cell type, while other types are very rarely seen (Fig. 2.99) [556]. Thyroid carcinomas are usually of the papillary and follicular types [559, 560]. Examples of colonic adenocarcinoma and of hepatocellular carcinoma metastatic to the sinonasal tract have been reported (Fig. 2.100) [561–566].
Differential diagnosis

Metastatic clear cell carcinomas have to be distinguished mainly from primary sinonasal clear carcinomas of minor salivary gland derivation [553]. Metastatic lung cell carcinomas, mainly those of small and intermediate cell type, have to be distinguished from their primary sinonasal counterparts [272]. Metastatic thyroid carcinomas have to be differentiated from primary sinonasal low-grade carcinomas tubulopapillary type [333]. Metastatic intestinal adenocarcinomas require precise distinction from primary ITAC [565]. Diagnostic difficulties usually arise with undifferentiated metastatic tumors, mainly those of unknown primary site of origin; clinical history, immunohistochemistry, and molecular techniques are in these instances of help.

Treatment and prognosis

For metastatic sinonasal tumors, palliative therapy is in most instances recommended. However, prognosis may depend on whether the metastasis is isolated or part of widespread disseminated disease. If the sinonasal metastasis is localized and treated aggressively, the average survival following its discovery may be as long as 20–30 months [555].

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