Chapter 1
The Etiology and Epidemiology of Sinonasal Malignancies

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Introduction

Sinonasal malignancies represent a highly diverse group of pathologies. Representing only 3–5% of head and neck cancers, their overall incidence is as low as 0.556/100,000 per year with a male to female ratio of 1.8:1 [1, 2]. A Surveillance, Epidemiology, and End Results (SEER) review study, conducted between 1973 and 2006, showed a relatively stable incidence rate of sinonasal malignancies overall during this period of time [1]. However, due to the rare nature of these tumors, large, prospective studies evaluating the etiology and epidemiology of the different malignancies occurring within the sinonasal cavity do not exist. We are thus limited to data acquired via population database analysis and relatively small retrospective case series.

Squamous cell carcinoma (SCC) is the most common pathology identified in North America [1], whereas adenocarcinoma is the most common found in Europe [2]. In general, tumors of epithelial origin account for approximately 80% of malignancies of the sinonasal cavity and anterior cranial base (ACB) [1]. The majority of tumors arise within the nasal cavity (43.9%) followed closely by the maxillary sinus (35.9%) [1]. The wide variety of pathologies confers variable oncologic behavior, often requiring multimodality treatment. Information regarding the etiology and epidemiology of the tumors described in this chapter is summarized in Table 1.1.

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Table 1.1 Etiology and epidemiologic factors for various sinonasal malignancies

Tumor type	Incidence (people per year)	Male:female	Mean age at presentation (years)	Most common location	Risk factors
Sinonasal squamous cell carcinoma	0.25/100,000	1.7:1	66	Maxillary sinus	Tobacco, alcohol, high-risk HPV subtypes
Nasopharyngeal carcinoma	Endemic: 20–50/100,000 Non-endemic: 0.4/100,000	2.6:1	40–70 (only average reported)	n/a	EBV, preserved salted fish, tobacco; Genetic/ethnicity-related: Chinese, Southeast Asian, Pacific Islander
Adenocarcinoma	0.44/100,000	1:0.5	64	Ethmoid	Environmental exposures: wood-dust, leather tanning, nickel, chrome, paint, varnishes, and glues
Adenoid cystic carcinoma	Incidence not reported	1:1.13	59.6	Maxillary sinus	c-Kit, possibly HPV
Olfactory neuroblastoma	0.4/100,000	1.4:1	50	Nasal cavity	Hedgehog pathway; Gene mutations: MYC, KDR, dystrophin, laminin alpha 2; chromosome copy number changes
Sinonasal neuroendocrine carcinoma	0.0077/100,000	1.8:1	53 (only median reported)	Nasal cavity vs. ethmoid	Possibly HPV
Sinonasal undifferentiated carcinoma	0.02/100,000	1.6:1	58	Nasal cavity	EBV is controversial, possibly HPV
Sinonasal melanoma	0.05/100,000	1:1.3	67	Nasal cavity	Gene mutations: BRAF, c-Kit, NRAS, HRAS, GNAQ, p16-CDK4-RB, ARF-p53, and PI3K-Akt
Chordoma	1/100,000	1:1	Mean not reported; majority in the sixth decade	Clivus	Gene mutations: Brachyury, p16-CDK4-RB, ARF-p53, and PI3K-Akt

Tumor type	Incidence (people per year)	Male:female	Mean age at presentation (years)	Most common location	Risk factors
Rhabdomyosarcoma	Incidence not reported; most common sarcoma of the head and neck (45%)	1:1	Mean not reported; majority in the first and second decades	Not reported.	Chromosomal alterations, subtype specific
Chondrosarcoma	Incidence not reported; 6% of sinonasal tumors	1:1	44.3	Petroclival synchondrosis	Radiation, radioactive isotopes, beryllium, zirconium, Lucite; malignant transformation of: enchondromas and exostoses
Ewing's sarcoma	Sinonasal not subclassified from head and neck in reports	1:2	32.4	Nasal cavity equal to sinuses	Chromosomal abnormality: 11:22 translocation
NK/T-cell lymphoma	0.032/100,000	Male predilection reported	Mean not reported; majority in the sixth decade	Not reported.	EBV, immune suppression; Genetic/ethnicity-related: endemic in Asian countries, common in South and Central America
Diffuse large B-cell lymphoma	0.06/100,000	1.2:1	65.8	Maxillary sinus	Immunosuppression, transformation of many low-grade B-cell lymphomas
HPV-related multiphenotypic carcinoma	50 cases reported	1:1.5	54	Nasal cavity	High-risk HPV

Squamous Cell Carcinoma

Sinonasal

The most common malignancy of the sinonasal cavity is squamous cell carcinoma (SCC), accounting for 60% of cases (Figs. 1.1, 1.2, and 1.3) [1]. The incidence has remained relatively stable over the past few decades in some studies, and declined in others. A European study, conducted in Denmark, reported a change in incidence from 0.7/100,000 in 1980 to 0.43/100,000 in 2014, which did not reach statistical significance [4]. In the United States, the incidence reported in a SEER database review from 1973 to 2009 showed a declined from approximately 0.4 to 0.25 per 100,000 over the study period [5].

These tumors are most commonly found within the maxillary sinus (60%) followed by the nasal cavity and ethmoids, and rarely in the frontal or sphenoid sinuses. There is a male predilection at approximately 63.6% [5]. SCC has several histologic variants including keratinizing (typically well differentiated), which represents 70% of cases, non-keratinizing (usually poorly differentiated) accounting for 20% of cases, and other variants accounting for 10% of cases (e.g., verrucous, basaloid, papillary, adeno-squamous, and spindle cell) [6]. Tumor behavior, treatment, and overall survival vary based on the histologic subtype [7]. A recent SEER database review of 4718 cases reported a male predominance for all histologic subtypes ranging from 67.3% to 77.6% [7]. The mean age at diagnosis for conventional SCC was 66.0 ± 13.3 standard deviation (SD) years with the only subtype reaching a statistical difference being basaloid at 61.8 ± 15.6 [7].

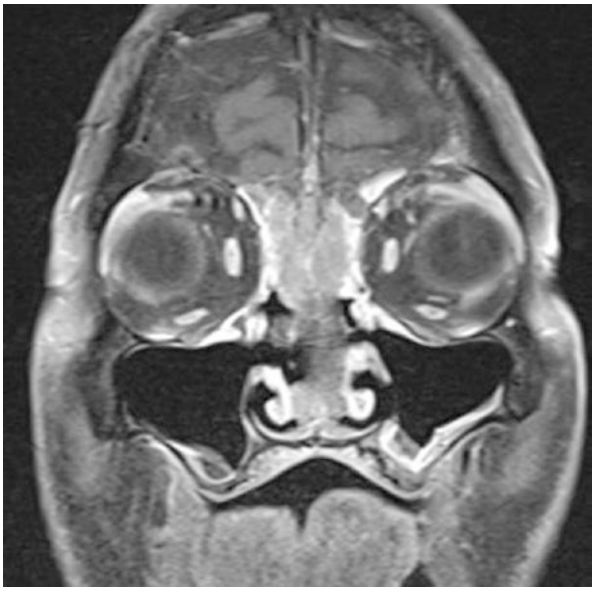

Fig. 1.1 MRI brain T1 post-contrast of a sinonasal SCC with involvement of the anterior cranial base

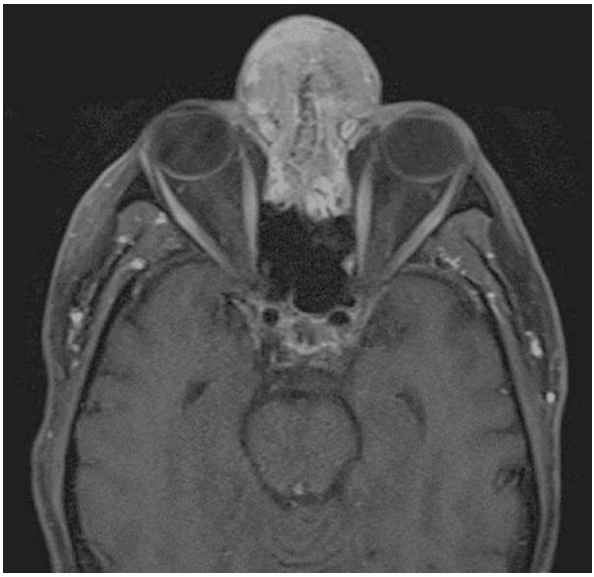

Fig. 1.2 MRI brain T2 FLAIR with contrast showing extensive involvement of the nasal soft tissues

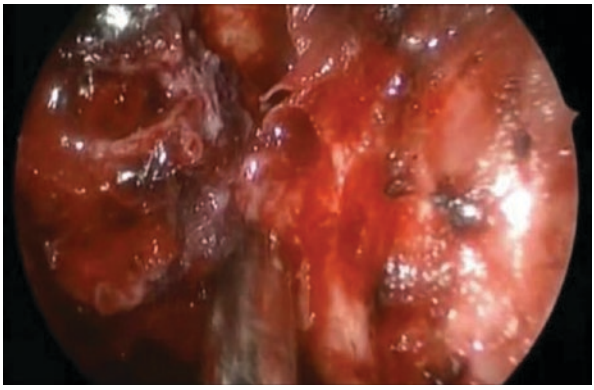

Fig. 1.3 Endoscopic endonasal view of the tumor attachment at the skull base

Risk factors for sinonasal SCC largely mirror those for all head and neck subsites. These include tobacco use, alcohol consumption, and infection with high-risk human papillomavirus (HPV) [8].

There remains a risk for development of sinonasal SCC with the environmental exposures discussed previously with adenocarcinoma, though to a lesser extent. Malignant degeneration of an inverted papilloma is also a well-established etiology of sinonasal SCC. The rate of transformation is reported to be approximately 10% [9]. The relationship between HPV, in particular HPV-18, and higher risk of malignant transformation has been emphasized but additional prospective studies are needed to fully define this relationship [10]. HPV has been identified to be transcriptionally active in up to 20–30% of sinonasal SCC tumors with reports of improved prognosis [11–13]. A recent National Cancer Database review of 770

patients with sinonasal SCC revealed 31.7% HPV-positivity [13]. These tumors were more likely to be found in younger patients, located in the nasal cavity, and high grade. On multivariate analysis, HPV-positivity remained a favorable prognostic factor. However, to date, there are no high-quality prospective studies elucidating the impact of HPV on treatment response and survival.

Nasopharyngeal

SCC arising from the nasopharynx is a distinct pathologic entity termed nasopharyngeal carcinoma (NPC). The majority of cases occur between 40 and 70 years of age, with a male to female ratio of 2.6:1 in endemic regions [14]. There is significant regional variability in the incidence of NPC. In the United States, the incidence is 0.4/100,000 persons; however in Southeast Asia, Southern China, and North Africa, NPC is considered endemic and the incidence is as high as 20–50/100,000 [15–17]. These rates have not remained stable over the past 40 years, with both endemic and non-endemic rates having shown a decline. For example, a retrospective review of the Hong Kong Cancer Registry including 21,768 cases of NPC revealed a decrease in incidence from 28.5/100,000 males in 1980–1984 to 20.2 in 1995–1999, and from 11.2/100,000 females to 7.8 [18]. This decline is likely attributed to a better understanding and avoidance of known environmental risk factors including exposure to volatile nitrosamines in preserved salted fish [14] and tobacco use, as well as increased screening of at-risk populations. In the United States, incidence also varies widely by ethnicity, which remains a strong predictor of NPC, suggesting a genetic predisposition in its etiology in addition to these culturally associated environmental risk factors. Highest incidence is seen in Chinese, followed by Southeast Asians and Pacific Islanders, and is low in Black and White Americans [17]. For example, certain human leukocyte antigen (HLA) genes have been found to confer an increased susceptibility for NPC (e.g., HLA-A2, HLA-B46), as well as genetic polymorphisms of some metabolic enzyme and DNA repair genes (e.g., CYP2E1, GSTM1, hOGG1, XRCC1) [17].

NPC has been histologically divided into three subtypes according to the World Health Organization (WHO). These include: keratinizing (WHO I), non-keratinizing (WHO II), and undifferentiated (WHO III) [19]. Epstein Barr Virus (EBV) is strongly associated with subtypes WHO II and III, and is associated with a favorable treatment response and prognosis [20]. The association of NPC and Epstein Barr Virus (EBV) has been well established and also shows regional variation (95% of endemic cases and as low as 40% of non-endemic cases) [21]. The etiology of non-endemic cases is likely to be more akin to other head and neck squamous cell cancers. Circulating blood plasma EBV DNA titers can be monitored for treatment response. Higher pretreatment titers show an association with worse overall survival and lower post-treatment titers show an association with better treatment response [22].

Adenocarcinoma

Sinonasal adenocarcinoma (SNAC) is the most common sinonasal malignancy in Europe, with the majority of cases arising in the ethmoid sinuses (85%). There are several different histologic subtypes including intestinal type (80%), non-intestinal type (10–15%), and salivary type (5–10%) [23]. It accounts for approximately 10% of all sinonasal malignancies [24] with a mean age at diagnosis of 62 years [25]. A single-institution review of 746 cases in the United States reported an incidence of 0.44/1,000,000, which has been relatively stable over the past 40 years [25]. Whereas, a retrospective review of the Netherlands Cancer Registry, including 536 cases of SNAC, reported a decrease in incidence from approximately 2.9/1,000,000 to 1 in men from 1989 to 2014 and stable incidence in women during this period at 0.5/1,000,000 [26].

Development of SNAC has classically been associated with environmental exposures to wood-dust, leather tanning, nickel, chrome, paint, varnishes, and glues [23, 24, 27]. This was presumed to account for a reported male predominance in European studies given the traditional occupational exposures; however, recent database reviews conducted in the Unites States report a near equal incidence between males and females [24]. It is unclear if environmental exposures play less of a role in these cases or if there has been a paradigm shift in gender distribution in the workplace.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is a malignant epithelial tumor of salivary gland origin with a propensity for perineural invasion. ACC accounts for <2% of head and neck malignancies [28]. Approximately 10–25% of cases arise in the sinonasal cavity, representing 6.2% of sinonasal malignancies, and are associated with a poorer prognosis than other head and neck subsites [1, 29, 30]. Histologically, ACC has been divided into three growth patterns: cribriform, tubular, and solid, with the latter representing the most aggressive form. A recent review of the National Cancer Database including 793 cases reported a slight female predominance (53.1% female to 46.9% male) and mean age of diagnosis of 59.6 years [30]. The most common primary site was the maxillary sinus (49.7%), followed closely by the nasal cavity (32.4%).

No distinct environmental risk factors have been identified; however, recent studies have shown that c-Kit mutations are associated with poorer prognosis and epidermal growth factor receptor expression is associated with improved survival [31]. Recent studies have also evaluated the association between ACC and HPV. Miller et al. obtained 23 primary tumor specimens between 1998 and 2013 and performed p16 testing using immunohistochemistry (IHC) as well as polymerase chain reaction (PCR) evaluation of E6/E7 [32]. Two specimens showed strong and diffuse p16

staining and 15 cases showed positivity isolated to luminal cells. Of the two diffusely positive specimens, only one was positive for HPV on PCR. Boland et al. evaluated 27 cases of ACC with IHC for p16 and fluorescent in situ hybridization (FISH) for HPV [33]. They reported 22 cases with focal p16-positivity and 3 cases (16%) with diffuse p16-positivity, two of which were also positive for high-risk HPV. Because of the rarity of this disease entity, obtaining a large sample size to further elucidate this relationship will be difficult; however, this study reports a low incidence of HPV-positivity [33].

Olfactory Neuroblastoma

Olfactory neuroblastoma (ONB) represents approximately 10% of sinonasal malignancies, arising from the neuroectodermal cells of the olfactory epithelium along the olfactory cleft [34, 35]. The incidence has been reported as 0.4/1,000,000 per year [36]. Histologically, they are categorized as one of the many "small blue cell" tumors with classically described Homer Wright rosettes and Flexner-Wintersteiner rosettes. They exhibit a highly variable range of oncologic activity, from low-grade indolent tumors to high-grade aggressive disease. Multiple recent meta-analyses and population-based studies have been performed, particularly looking at treatment strategies and outcomes. These studies have reported a slight male predominance (58–59% vs. 41–42%) and mean or median age in the 50s [37, 38]. Primary tumor location was most frequently found in the nasal cavity (83%) followed by the ethmoid sinus (9%) [38].

ONB has not been associated with any specific environmental risk factors; however, research has identified specific genetic factors that may play a role in tumorigenesis and development of metastatic disease. Research on the development of ONB has shown involvement of the sonic hedgehog pathway, MYC, and KDR genes, the latter two likely involved in metastatic progression, in additional to many others [39, 40]. Gallia et al. found the presence of mutations in dystrophin (12/14 cases) and laminin alpha 2 (1/14 cases), reporting 93% of the tumors evaluated having mutations in genes related to muscular dystrophy [41]. Several studies have reported chromosome copy number changes including gains at 7q11 and 20q and deletions at 2q, 5q, 6p, 6q, and 18q [42].

These studies point to the complex molecular processes that are responsible for the development of ONB.

Sinonasal Neuroendocrine Carcinoma

Neuroendocrine tumors show overlapping morphologic and immunohistochemical features regardless of site of origin, and have been found across all visceral subsites [43]. Sinonasal neuroendocrine carcinomas (SNECs) are an exceedingly rare group of sinonasal malignant neoplasms with aggressive histopathology. They represent

3–5% of all sinonasal malignancies and have a high rate of metastatic spread [43, 44]. The overall incidence of SNEC reported in a recent SEER database review of 201 cases was 0.012/100,000 in 1986 and 0.0077 in 2011; however, the change did not reach statistical significance [45]. Rarely, these tumors present with paraneoplastic syndromes including hormones such as ACTH and calcitonin [43].

SNEC is histologically further subdivided by grade of differentiation. Well-differentiated tumors are referred to as carcinoid and moderately differentiated tumors are referred to as atypical carcinoid. Poorly differentiated tumors tend to be aggressive with poor prognosis and are further categorized as small-cell (small-cell SNEC) and large-cell variants (large-cell SNEC) [35]. Large-cell SNEC is often denoted as sinonasal undifferentiated carcinoma (SNUC) in the literature, though SNUC more likely represents a combination of completely de-differentiated tumors arising from a variety of different lineages.

A recent meta-analysis of SNEC included 701 cases, though many of these had ambiguous classification between large-cell SNEC and SNUC [46]. The median age of presentation was 53 years with an overall male gender predilection (64.6%). This was consistent with the findings in the previously discussed SEER database review [45]. Most patients presented with advanced disease, making designation of tumor origin difficult, though prior studies report the nasal cavity or the ethmoid sinus as the most common site [47, 48]. Ten cases (1.4%) showed ectopic hormone development including ACTH, beta-MSH, calcitonin, serotonin, or ADH. These included cases of small-cell SNEC and well- or moderately differentiated SNEC.

SNEC has no known environmental risk factors [49]. A few small retrospective studies have shown HPV-positivity in small-cell SNECs [50, 51]. However, further studies with a larger sample size are required to draw any conclusion on the association between HPV and SNEC.

Sinonasal Undifferentiated Carcinoma

Sinonasal undifferentiated carcinoma (SNUC) is another rare sinonasal malignancy with an aggressive growth pattern and very poor prognosis. It represents 3–5% of sinonasal cancers with an annual incidence of 0.02 per 1,000,000 [34, 52]. Hallmark histologic features include a high mitotic rate, necrosis, lymphovascular invasion, and lack of distinct cellular differentiation [35]. As stated previously, they tend to be associated with sinonasal neuroendocrine carcinomas though likely represent a more diverse grouping of de-differentiated carcinomas. Two recent SEER database reviews performed by Ahn et al. and Kuan et al. reported on 112 cases and 328 cases of SNUC, respectively [53, 54]. A male predilection was identified in both studies (approximately 61% male to 39% female in both studies). Most patients were diagnosed between the ages of 40 and 60 years with a mean of 58. The most common primary subsite was the nasal cavity (38% and 29.3%, respectively) followed by the maxillary sinus (21% and 27.4%, respectively).

There are no known environmental risk factors for SNUC. EBV has been reported in SNUC; however, this topic presents significant heterogeneity in the literature. It

has been proposed that EBV-positivity in some studies is due to the inclusion of non-SNUC high-grade malignancies, and strict histologic criteria are necessary to avoid confusion [55, 56]. HPV expression has also been recently investigated using p16 and HPV DNA. A small case series of five patients revealed strong, diffuse positivity for p16 in all five cases; however, HPV DNA was not detected [57]. Further investigation is required on larger sample sizes in order to define this relationship.

Sinonasal Melanoma

Sinonasal melanoma (SNM) is an aggressive malignancy of neural crest-cell-derived melanocytes with poor prognosis. They represent 4% of all head and neck melanomas and approximately 3.5% of all sinonasal malignancies [58]. They have significant epidemiologic differences from cutaneous melanoma (CM) including a later mean age of presentation (67 years for SNM vs. 55 years for CM), higher percentage of advanced disease at presentation, and amelanotic appearance [59]. They also lack the environmental risk factor of sun exposure intrinsic to CM. Two recent SEER database reviews evaluating 304 [60] and 567 [61] cases of SNM showed a slight female predilection of 56.3% and 57.4%, respectively, with an annual incidence of 0.05/100,000. The average age at diagnosis was 71.2 and 69 years with the nasal cavity being the most common primary site (65.5% and 67.5%) followed by the maxillary sinus (15.1% and 16.9%).

Though SNM lacks any known environmental risk factors, genetic alterations likely play a substantial role in tumor development. Alterations in oncogenes and tumor suppressor genes are the hallmark of neoplastic transformation in melanocytic tumors. Somatic mutations of BRAF, NRAS, HRAS, and GNAQ oncogenes act primarily by inducing cellular proliferation via the MAP-Kinase pathway [62]. Abnormalities in tumor suppressor genes such as p16-CDK4-RB, ARF-p53, and PI3K-Akt promote dysregulation is additional pathways leading to tumorigenesis [62]. The presence of these mutations is highly variable between tumor subsites requiring specific evaluation of sinonasal melanoma cases. BRAF mutations are classically associated with melanoma, with approximately 75% of cutaneous melanomas expressing this oncogene. However, mucosal melanomas are rarely associated with this mutation, and thus have poor response to BRAF-mutation-targeted therapies [59, 62]. Turri-Zanoni et al. performed direct sequencing of 32 primary sinonasal melanomas to identify molecular abnormalities specific to this subtype [62]. The majority of cases lacked BRAF mutations (97%), with the classically described V600E mutation being absent in all cases. NRAS mutations were found in 22% of cases and KIT mutations in 12.5%. Furthermore, PTEN and p16/INK4a tumor suppressor genes were evaluated and loss of expression was found in 48.1% and 55.2% of cases, respectively. This complex array of abnormalities appears to lead to diffuse activation of the PI3K/Akt and RAS-MAPK pathways found in 100% of cases. In addition, chromosomal alterations commonly found in cutaneous melanoma were also found in many of the SNM cases.

Chordoma

Chordomas are primary bone neoplasms that originate from embryonic notochord remnants, most commonly arising in the clivus in the head and neck region. The annual incidence is approximately 1/100,000 people [2]. The mean age at presentation of cranial chordomas is in the sixth decade, with a wide range including the pediatric population [2, 63]. A recent meta-analysis of 467 patients reported an age range from 2 to 87 years, with an equal male to female ratio [64]. Chordomas account for 1–4% of all primary malignant bone tumors and those originating in the clivus account for 35–49% of all chordomas [63, 65]. They represent a rare entity, accounting for only 0.1% of all ACB malignancies [64]. These tumors tend to be locally destructive with a high rate of local recurrence and cranial nerve or intracranial involvement [64]. Histologically, they are comprised of physaliferous cells with a classic "soap bubble" appearance.

There are no known environmental risk factors for chordoma, though genetic factors likely play a role in tumor development. Brachyury is a gene classically associated with chordoma, which represents a normally inactive transcription factor for notochordal development that is aberrantly re-expressed [63]. Brachyury may be considered a driver oncogene in the development of chordoma. Recent advances in the molecular understanding of the pathogenesis of chordomas have led to the identification of promising targetable pathways [63]. These include the mTOR, EGFR, VEGF, PDGFR, and PD/PDL pathways, which are currently under investigation [63].

Sarcoma

Sarcomas arising in the head and neck have a reported incidence of 1.59/100,000 and those arising in the sinonasal cavity and ACB are even more rare [66]. They represent a histologically diverse group of neoplasms, mostly arising from mesenchymal tissue. The most common sarcomas in this anatomic region include: rhabdomyosarcoma (RMS), chondrosarcoma, and Ewing's sarcoma.

Rhabdomyosarcoma

Rhabdomyosarcomas (RMSs) are comprised of malignant skeletal muscle cells called rhabdomyoblasts and should be considered in the differential of any small round cell malignancy. They account for approximately 8% of all pediatric sarcomas and 2–5% of all adult sarcomas [67]. It is the most common sarcoma to occur in the head and neck region (45% of cases). There is no defined sex predilection and they most often occur in the first and second decades of life [67]. The most common

histologic types of RMS in the head and neck region are: embryonal type (71%), alveolar type (13%), and botryoid subtype of embryonal (2%) [68].

RMSs are associated with multiple chromosomal alterations that are specific to each histologic type [68]. For example, embryonal RMS can show loss of heterozygosity of chromosome 11p15.5, and fusion transcripts of PAX3/FKHR and PAX7/FKHR. Alveolar RMS can show multiple different translocations, most commonly t(2;13)(q36;q14) as well as PAX3/FKHR fusion transcripts in 80–90% of cases. Botryoid variants show multiple chromosomal abnormalities including deletion of the short arm of chromosome 1, trisomies of chromosomes 13 and 18, duplication of chromosome 8, or loss of chromosome 11 [68, 69].

Chondrosarcoma

Chondrosarcomas arise from hyaline cartilage, and are classically found in the ACB at the petroclival synchondrosis or foramen lacerum, and in the maxillary or ethmoid sinuses. They account for approximately 6% of ACB and sinonasal tumors [70]. In general, they display a slow, indolent progression though this is varied based on histologic grade [44]. Histologically, they are comprised of large multinucleated cells with a background of cartilaginous matrix. They lack the classic physaliferous cells found in chordoma, assisting with the diagnosis. A recent SEER database review of 226 patients reported a mean age at diagnosis of 44.3 years (range 1–82) with an equal male to female ratio [70].

Various physical and chemical agents have been shown to cause chondrosarcoma, of varying anatomic locations, including irradiation, radioactive isotopes, beryllium, zirconium, and Lucite [71]. They have also been known to arise from pre-existing benign bony or cartilaginous tumors including Maffucci syndrome, which is characterized by multiple enchondromas; multiple exostoses caused by a mutation in one of three genes EXT1, EXT2, or EXT3; Paget's disease; or in Ollier disease, also involving multiple enchondromas [72].

Ewing's Sarcoma

Ewing's sarcomas represent a spectrum of poorly differentiated sarcomas of combined neuroectodermal and mesenchymal origin that commonly present in the pediatric population. They are further categorized as osseous and extraosseous Ewing's sarcoma, peripheral neuroectodermal tumor (PNET), and Askin's tumor of the chest wall [73].

Histologically, they should be considered in the differential of any small round blue cell tumor. Tumors originating in the head and neck region are uncommon (1–18%) and primary sinonasal tumors are even more rare and typically not subclassified in studies [73–75]. A retrospective case series of 14 patients reported a

male to female ratio of 1:2, with mean age of presentation of 32.4 years (range 7–70) [73]. Tumor site of origin was equal between the nasal cavity and sinuses.

The vast majority of tumors are associated with a specific 11:22 translocation, which is a reciprocal translocation of the EWSR1 and FLI-1 genes [76].

Lymphoma

Non-Hodgkin lymphoma of the sinonasal cavity is the second most common primary malignancy of the head and neck after SCC [77]. They include lymphomas of B-cell, T-cell, and NK/T-cell lineages, the most common being extranodal (nasal type) NK/T-cell lymphoma [78]. The majority of NK/T-cell lymphomas occur in the nasal cavity and B-cell lymphomas in the paranasal sinuses [67]. B-cell lymphomas occurring at this site include: diffuse large B-cell lymphoma, Burkitt lymphoma, extranodal marginal B-cell lymphoma of the MALT type, and follicular lymphoma with diffuse large B-cell being the most common. Here we will review the two most common subtypes including NK/T-cell lymphoma and diffuse large B-cell lymphoma.

NK/T-Cell Lymphoma

NK/T-cell lymphoma, previously referred to as lethal midline granuloma, involves a high destructive process of the midfacial region. A recent SEER database review of 328 cases reported an annual incidence of 0.032/100,000 with a statistically significant increase in incidence from 2000 to 2011 [79]. These tumors arise from predominately a natural killer cell origin though a small percentage of them are of T-cell lineage [77]. It has a male predilection and typically presents in the sixth decade of life [78, 79]. It also shows geographic variations and is endemic in many Asian countries, though is also frequently reported in South and Central America as well as Mexico in individuals primarily of Native American origin [67, 77]. Histologically, it contains a polymorphic cell population along with atypical cells with high mitotic activity, which are angio-invasive. Regardless of ethnic background, it has a strong association with EBV, which is present in >95% of cases [78]. There is also a small increased risk with immune-suppressed states.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma is the most common sinonasal lymphoma, though they are still a rare entity. Histologically, they are made up of mature B-lymphocytes with enlarged nuclei. The annual incidence has been reported as low as 0.06/100,000

[80]. A recent SEER database review of 852 cases reported the average age at presentation of 65.8 years with a male to female ratio of 1.2:1 and a predilection for Caucasians (80.9%) [80]. The most common anatomic site was the maxillary sinus (36.8%) followed closely by the nasal cavity (34.0%). An increased risk is associated with immunosuppression including post-transplantation and human immunodeficiency virus infection, and is classified as an AIDS-defining illness [78]. It may arise de novo or from the transformation of one of many low-grade B-cell lymphomas [77].

HPV-Related Multiphenotypic Sinonasal Carcinoma

HPV-related multiphenotypic sinonasal carcinoma (HMSC) is a newly described entity with only 50 cases having been reported in the literature. This tumor is always associated with high-risk HPV infection [81]. It was previously referred to as "HPV-related carcinoma with adenoid cystic like features," though its expanded morphologic spectrum has led to its current name change. Histologically, it resembles adenoid cystic carcinoma with additional myoepithelial, ductal, and squamous differentiation and other unique features including sarcomatoid transformation and even cartilaginous differentiation.

Though few cases have been reported, there appears to be an increased prevalence in Caucasians and has a 1.5:1 female to male ratio [82, 83]. The mean age at presentation is around 54 years with a broad range from 20 to 90 years. It is most commonly confined to the nasal cavity or involves the maxillary and ethmoid sinuses. Though it may display high-grade histologic features, it tends to exhibit indolent clinical behavior [81] (Fig. 1.4).

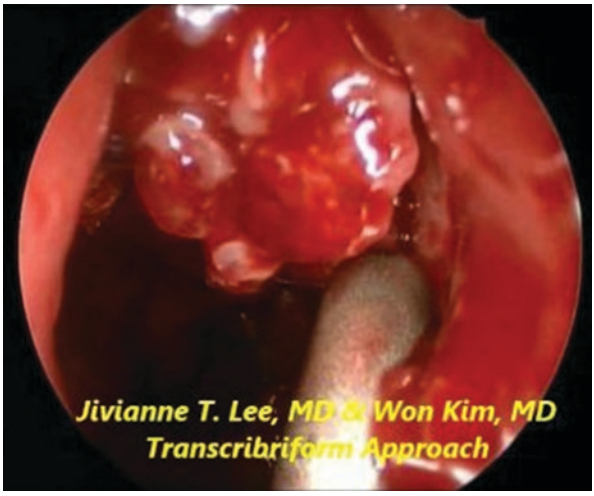

Fig. 1.4 Endoscopic view of an HPV-related multiphenotypic sinonasal carcinoma within the ethmoid sinuses

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