

# 2019 AAOMP SEMINAR

**INTERCONTINENTAL HOTEL**

**MIAMI, FLORIDA**

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## Case Histories

- 1) 65 year old female with a lesion on the buccal mucosa. Clinical impression - "metastatic carcinoma since patient has history of bone cancer".
- 2) A 7 year old female with 3 X 2 cm tumor mass of right buccal mucosa. Well defined. One year duration.
- 3) A 44 year old female presented with an intraosseous lesion of right frontal and malar bones. The lesion resulted in ipsilateral exophthalmos.
- 4) A 47 year old presented with a nodular firm ulcerated 3+cm growth on the right mandibular alveolar ridge. Minor resorption of the superior border of the ridge was seen.
- 5) A 15 year old female presented with an asymptomatic, progressive swelling of the left maxilla for 4 months' duration. The patient denies any constitutional symptoms and is otherwise healthy. Her general dentist prescribed antibiotics; she showed no improvement and an incisional biopsy was performed.
- 6) 18 year old male referred for extraction of wisdom teeth. Noted to have asymmetrical expansion of right proximal portion of mandibular foramen. Biopsy negative at outside facility. This sample represents sample of the radiographically ill-defined mass in right pterygopalatine fossa.
- 7) 65 year old female with expansile palate/maxillary sinus mass.
- 8) A 63 year old white male presented with a palatal mass with bone destruction and oro-antral communication.
- 9) 74 year old male presented with a large residual non-healing bony defect with significant bleeding after extraction of tooth #2.
- 10) A 33 year old male with an expansile lesion of the left posterior mandible, noted by the patient only a month ago.

## CASE 1.

### DIAGNOSIS: METASTATIC ENDOMETRIAL ADENOCARCINOMA, ENDOMETRIOID TYPE

Endometrial adenocarcinoma is a carcinoma of the uterus and the most common malignancy of the female genital tract in the United States<sup>1</sup>. The majority of affected patients are over the age of 50 years, and only 5% of patients develop endometrial adenocarcinoma younger than age 40<sup>2</sup>. Although the cause is unknown, most cases demonstrate alterations in molecular processes or pathways, including in DNA mismatch repair, chromatin remodeling, PIK3CA, Wnt/ $\beta$ -catenin, KRAS, or FGFR2. Sporadic mutations in TP53 and PTEN appear to play a significant role in many of these tumors. Patients with Cowden or Lynch syndromes are at a higher risk of developing this type of malignancy. Additional risk factors include nulliparity, prolonged estrogen exposure without progesterone therapy (unopposed estrogen therapy), Tamoxifen use, estrogen-producing tumors, polycystic ovary syndrome, higher numbers of menstrual cycles during a lifetime, history of breast cancer, family history of endometrial adenocarcinoma, cigarette smoking, and excessive conversion of androgens to estrones in patients with obesity<sup>1-3</sup>. Combined oral contraceptive use, medoxyprogesterone use, and levonorgestrel intrauterine contraceptive devices tend to be protective factors against endometrial carcinoma<sup>2</sup>.

Endometrial carcinoma is divided into two clinicopathologic types, including endometrioid and non-endometrioid types, and nine different histopathological subtypes: 1.) endometrioid, 2.) mucinous, 3.) serous, 4.) clear cell, 5.) mixed cell, 6.) squamous cell, 7.) transitional cell, 8.) small cell, and 9.) undifferentiated<sup>2</sup>. The patient in this case was diagnosed with endometrioid clinicopathologic type, the most common type, comprising approximately 75% of all uterine cancers<sup>2</sup>.

Histopathologically, endometrioid type endometrial carcinoma mimics glandular tissue of healthy endometrium and may be well-to-poorly differentiated<sup>4</sup>. The presence of shadow cells, also known as ghost cells, in this case provided an intriguing challenge because of the proximity of the metastatic lesion to the tooth-bearing regions of the jaws and association of ghost cells with odontogenic cysts and tumors. Entities known to demonstrate shadow cell differentiation include calcifying odontogenic cyst/calcifying cystic odontogenic tumor/dentinogenic ghost cell tumor, odontogenic ghost cell carcinoma, pilomatricoma, craniopharyngioma, endometrial hyperplasia or carcinomas, teratomas, colorectal carcinomas, neuroendocrine carcinomas of the gallbladder, and urothelial carcinomas<sup>5-8</sup>. Focal accumulations have also been identified in other odontogenic neoplasms, such as ameloblastoma, adenomatoid odontogenic tumor, and odontomas<sup>8</sup>. In addition to the molecular alterations noted above, the presence of ductal structures and positivity to some or all of the following immunohistochemical markers differentiate these various shadow cell tumors from endometrioid carcinoma: ER (estrogen receptor), PR (progesterone receptor), p53, PAX8, and p16<sup>2,9</sup>.

Metastatic lesions for FIGO (Federation of Gynecology and Obstetrics) grade 1 or 2 tumors with a tumor size of less than 2cm, less than 50% of myometrial invasion, and well-differentiated histology, demonstrate a very low risk of metastasis<sup>2</sup>. One of the most important prognostic factors and factors that indicates risk of metastasis is the extent of myometrial invasion at the time of diagnosis<sup>10</sup>. When endometrial carcinoma does metastasize, the most common locations are to the intra-abdominal or inguinal lymph nodes, lung, liver, bone, and/or peritoneum<sup>2</sup>. Metastasis to the oral cavity is extremely rare. A 2013 case report of oral metastasis of endometrial carcinoma to the retromolar pad cites that only 12 cases of metastatic endometrial carcinoma to the oral cavity (including that case) had been reported<sup>11</sup>.

Treatment for endometrial carcinoma typically consists of a total hysterectomy, bilateral salpingo-oophorectomy, and comprehensive surgical staging, although fertility-sparing therapy may be an option for patients younger than age 35<sup>2</sup>. Women diagnosed with Lynch syndrome are carefully monitored until treated with the aforementioned prophylactic surgeries after child-bearing years<sup>2</sup>. When utilized, the recommended chemotherapeutic agents are carboplatin, paclitaxel, and/or trastuzumab or a variety of single chemotherapeutic agents. Radiation may be used as palliative therapy or in combination with chemotherapy. The overall 5-year survival rate for endometrial adenocarcinoma, regardless of grade, stage, or type, is 80%<sup>2</sup>.

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## CASE 2

### CELLULAR NEUROTHEKEOMA / PLEXIFORM FIBROHISTIOCYTIC TUMOR

Neurothekeomas (NTK) were first described in 1969 as nerve sheath myxomas by Hatking and Reed and later renamed as neurothekeomas in 1980 by Gallagher and Helwig, initially thought to be of neural origin. Cellular neurothekeoma (CNTK), was a name coined by Rosati et al in 1986. The name of this variant was proposed as its name implies, because are more cellular tumors showing a significant lesser amount of myxoid stroma. NTK's in general are dermal tumors with a predilection for the head and neck region and the upper extremities, but infrequently, cases had being described in the oral cavity and hypopharynx.

Historically, plexiform fibrohistiocytic tumors were described by Enzinger and Zhang in 1988 as a distinctive entity, describing 65 cases in their original publication. An excellent update on this tumor was published later in 2007, by Moosavi et al, which added 66 new cases from the AFIP. Interestingly, these authors explored the relationship between PFHT and CNTK. This article was published in honor of Franz M. Enzinger M.D., and to commemorate the 20<sup>th</sup> anniversary of the original description of PFHT. These authors suggested a probable relationship between these two entities, PFHT and CNTK, something which was originally suggested by Requena and Sanqueza in 1995, and subsequently suggested by Jaffer et al and also by Laskin et al in 2000. Furthermore, Enzinger and Weiss in their book, *Soft Tissue Tumors*, mention that sometimes differentiating CNTK from PFHT could pose a problem.

Epidemiologically, both lesions share identical features, affecting young patients, similar location, with female predominance and almost exclusively located in dermal / subcutaneous tissue. Microscopically, both tumors show plexiform architecture, spindle cells and histiocytoid cells with osteoclast type multinucleated giant cells, cellular pleomorphism, occasional mitotic figures and rarely, vascular invasion (not necessarily related to metastasis). The immunohistochemical profile is also similar or even identical, expressing SMA, CD68, CD57, S100A6, and occasionally focal CD34. The value of the expression of microphthalmia transcription factor (MiTF) is still a matter of debate, as some authors, including the Fox-Billings group, found that MiTF is present only on CNTK but negative in PFHT (histiocytoid predominant). However, Mohanty and associates found that MiTF is typically present in benign fibrohistiocytic lesions in general, suggesting that MiTF is perhaps too promiscuous. S100 is generally negative or only focal, in neural elements, probably representing residual fibers trapped within the lesion. The main difference according to the literature is behavior, as few cases of PFHT recurred and are related to regional lymph node metastasis, the latter being an extremely rare phenomena, but nevertheless, requiring long term follow up. Nevertheless, overall prognosis is excellent with a survival rate close to 100%. In contrast, CNTK is non recurrent and prognosis is excellent. This is the reason some authors consider PFHT as a borderline or even a low grade malignancy. However, on page 319 of the Moosavi et al paper, the authors imply that differences in clinical behavior between CNTK and PFHT may have being exaggerated (considering location and stage/size), and both lesions perhaps have similar clinical behaviors.

It is important to consider that few cases of CNTK of the oral cavity had been previously reported in the literature, but to best of my knowledge and based in an in depth literature review, to this date, there are no cases of PFHT reported in this specific location. However, based on the current evidence, both lesions are classified within the spectrum of myofibroblastic tumors, and most likely represent the same lesion, being almost impossible to differentiate between both, based on histomorphology or IHC profile. Future chromosomal studies may provide conclusive evidence to solve this issue.

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## Case 3

### EXTRACRANIAL CHORDOID MENINGIOMA

Meningiomas are benign neoplasms derived from meningotheial (arachnoid) cells, representing 20 to 36% of all intracranial tumors. Extracranial / extradural meningiomas represent 1 to 2 %. Histologically, meningiomas in general show whorled, epithelioid, syncytial architecture. Intranuclear inclusions are common. Even psammoma bodies or pre-psammoma are common but these are not present in all subtypes. The most common histologic variants are meningotheial and psammomatous. Chordoid meningiomas (CMs) are rare, representing 0.5 % of all subtypes, with a higher incidence in young patients and often associated with Castleman's disease. CMs bear a striking similarity to chordoma. CMs associated with Castleman's syndrome, tend to present a lymphoplasmacytic cell infiltrate. CM has a more aggressive clinical course and is assigned as WHO grade II. Slightly over 280 cases had being published in the literature, with most of them in an intracranial or spinal location. CMs are associated with a high recurrence rate, particularly in cases with subtotal resection. Gross total resection is the strongest predictor of tumor control. Although most meningiomas occur in the cranial, orbital or spinal regions, this tumor can also infrequently arise in extracranial locations, thus, potentially posing a diagnostic challenge, as they may have similar histology to other neoplasms, which have different biologic behavior and different therapeutic protocols. Histologically CMs are composed of cords and nests cells with an epithelioid

appearance, often showing intranuclear vacuoles, and eosinophilic cytoplasm. Tumor cells are embedded in an abundant mixoid or mucinous appearance matrix. The typical whorled appearance of meningiomas may be observed focally. IHC is positive for vimentin, EMA, Glut-1, progesterone receptors and Claudin-1. Cam5.2 can be focally positive. The middle age female patient presented here, did not have associated Castleman's syndrome.

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## Case 4

### SMALL CELL NEUROENDOCRINE CARCINOMA, METASTATIC (LUNG)

Neuroendocrine carcinomas are high grade malignant neoplasms with epithelial and neuroendocrine differentiation, uncommonly found in the head and neck area. Synonyms include poorly differentiated (Grade III) neuroendocrine carcinoma, oat cell carcinoma and small cell carcinoma of neuroendocrine type. <sup>1</sup> Two subtypes recognized are small cell neuroendocrine carcinoma (SmCC) and large cell neuroendocrine carcinoma (LCNEC). Neuroendocrine carcinomas are rare in salivary glands; however, when in salivary parenchyma, they primarily involve the parotid (80%) and are SmCC. <sup>2</sup>

Neuroendocrine carcinomas account for the second most commonly found neuroendocrine of the larynx (supraglottis), 0.5% of all laryngeal carcinomas and approximately 3% of sinonasal tumors. Laryngeal neuroendocrine carcinoma is more common in older men (median age 60 years) with a 2-4:1 male to female predilection. Sinonasal neuroendocrine carcinomas have a predilection for middle-aged men with a mean age of 40-55 years. <sup>1</sup> Neuroendocrine carcinomas account for approximately 3% of sinonasal tumors and when involving the nasal cavity, paranasal sinuses or skull base, the most common location is the ethmoid sinus. Primary neuroendocrine carcinomas of the head and neck often present with non-specific symptoms of nasal obstruction, discharge, sinusitis, laryngeal hoarseness, and/or dysphagia and have advanced local disease with regional or distant metastases (lung, liver or bone). <sup>1</sup> Clinically, tumors are often large and destructive with hemorrhage and necrosis. Oral lesions may present as a rapidly enlarging painless mass +/- surface ulceration. Cervical lymphadenopathy and facial nerve paralysis are common findings. <sup>2</sup>

Histologically, SmCC is characterized by infiltrative sheets, nests, cords and trabeculae of closely packed small to medium-sized cells with round-oval and/or spindled nuclei, fine granular chromatin, indistinct nucleoli, indistinct cell borders and minimal cytoplasm. Numerous mitoses, apoptosis and necrosis are present. Occasional neural-type rosettes and crush artifact may be observed. Perineural and lymphovascular invasion are common findings. <sup>1,2</sup>

Immunohistochemistry (IHC) is of great importance in differentiating SmCC from other lesions within the differential diagnosis. SmCC demonstrates positive reactivity with pancytokeratins, AE1/AE3, CAM5.2, EMA, synaptophysin, chromogranin, CD56, NSE and +/- with P63 (focal to scattered positivity). SmCC is negative with S100. <sup>2</sup>

Differential diagnoses for SmCC include basaloid squamous cell carcinoma (SCC), adenoid cystic carcinoma (solid type), malignant lymphoma, melanoma and Merkel cell carcinoma <sup>2,3</sup>. Basaloid squamous cell carcinoma is consistently reactive for pancytokeratins and high-molecular weight cytokeratins, with patchy expression of low molecular weight cytokeratins. P63 is diffusely and strongly reactive, and EMA is positive in the majority of cases. Basaloid SCC does not show punctate paranuclear reactivity seen in SmCC and will demonstrate CK7 and CK20 negativity. The identification of myoepithelial differentiation in the tumor as well as negativity for neuroendocrine markers, chromogranin and synaptophysin, will aid in distinguishing solid adenoid cystic carcinoma from SmCC. CK positivity and negative CD45 expression excludes malignant lymphoma. Negativity for S-100 and HMB-45 would exclude melanoma. Metastatic Merkel cell carcinoma demonstrates CK20 and Merkel cell polyoma virus (MCPyV) positivity and would require clinical and radiographic evaluation with a negative medical history of a previous malignancy. <sup>2</sup>

A recent IHC marker INSM1 (Insulinoma associated protein 1) is a nuclear marker of neuroendocrine differentiation with equivalent or better sensitivity and specificity compared to synaptophysin, chromogranin and CD56. This may aid the pathologist in the diagnosis of high grade neuroendocrine carcinoma that is negative for synaptophysin and chromogranin.<sup>4</sup>

As SmCC is a very aggressive malignancy with mean survival for head and neck sites at 14.5 months with an estimated 5-year survival rate of 13%.<sup>5</sup> Primary oral SmCC is extremely rare (less than 10 cases documented in literature) and treated surgically with adjuvant chemotherapy.<sup>6</sup> Salivary SmCC often utilizes surgical resection with lymph node dissection and adjunctive radiotherapy, although 50% of patients develop local recurrence and metastasis.<sup>2</sup> Prophylactic cranial irradiation (PCI) has shown a decrease in brain metastasis with head and neck SmCC, increasing the 3-year survival rate to 20.7%.<sup>7</sup>

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## Case 5

### MESENCHYMAL CHONDROSARCOMA

Mesenchymal chondrosarcoma (MC) represent up to 10% of all chondrosarcomas and can involve craniofacial bones or soft tissues in the head and neck region. They present across a wide age range with a peak in the second decade of life.<sup>1</sup> There is likely no gender predilection, though 1 series of sinonasal MCs showed a 9:4 female:male ratio.<sup>2</sup> MCs are most commonly encountered in the axial skeleton and femur, though up to one third of tumors present extraskelentially.<sup>1,3</sup> In the head and neck region, the jaws are the most common location for MCs to occur. Patients may present with pain, swelling, malocclusion, facial deformity, or nasal obstruction.<sup>1,3</sup> Radiographically, MCs present as an aggressive, lytic lesion with a poorly defined periosteal reaction that tends to both erode and expand the bone. Up to a third of cases may have calcification present.<sup>1,3-4</sup>

The histopathology reveals undifferentiated sheets of small round blue cells interspersed by islands of chondroid material; the mesenchymal cells are spindled in areas. The malignant cells show a tendency to cluster around intratumoral blood vessels in hemangiopericytoma-like fashion.<sup>1,5</sup> SOX9 appears to be both sensitive and specific for MC when compared to other small round blue cell tumors. MCs show INI-1 retained nuclear staining; most MCs will stain positively with NKX2.2 and S-100 in cartilaginous areas.<sup>5-8</sup> Desmin stains show variable positivity. MC round cells are negative for CD3, CD20, FLI-1, pankeratin, and CD34, amongst others.<sup>3,7</sup> Some reports indicate MCs do not react with CD99 staining, though others indicate positivity.<sup>3,5-6,8</sup> Notably, a characteristic HEY1-NCOA2 fusion gene has been identified.<sup>9</sup>

The treatment of choice for MCs of the jaws is surgery; en bloc resection should include a wide margin of healthy tissue beyond the tumor. Preoperative radiation therapy may be utilized prior to resection and is standard post-operatively; chemotherapy with doxorubicin and ifosfamide or cisplatin may also be used for unresectable tumors. Most patients develop local recurrences or metastasis within 5 years, though late recurrences may occur with MCs.<sup>3</sup>

The prognosis for MC is variable; overall, there appears to be a 55% 5-year survival and 27% 10-year survival. MCs of the jaws appear to have a better prognosis with a 5- and 10-year survival of 82% and 56%, respectively.<sup>1,10-11</sup> Patients with localized disease treated with surgery have the longest survival times and use of chemotherapy was associated with a decreased risk of recurrence and death.<sup>3</sup> Children, adolescents, and young adults have been reported to have an increased chance of survival.<sup>12</sup>

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## CASE 6

### DIAGNOSIS: NEUROMUSCULAR CHORISTOMA/HAMARTOMA

Neuromuscular choristoma/hamartoma (NMC) is a rare benign peripheral nerve lesion in which well differentiated skeletal muscle fibers are intimately associated or admixed with mature nerve fibers, infiltrating between and around nerve fascicles.[1-3] Originally designated neuromuscular hamartoma, the term neuromuscular choristoma was subsequently suggested in 1983 by Bonneau et al., since skeletal muscles are not normally found within nerve fibers.[2]

The origin of NMC has not been precisely clarified and a malformative event, resulting from aberrant differentiation is suspected, and NMC is unlikely to represent a true neoplastic growth.[4, 5] Many cases present in childhood and are located along major nerves or involving a nerve plexus of limbs, gut, head and neck. NMC of the head and neck have been identified in orbit, larynx, internal acoustic canal and gnathic bones. Involvement of the trigeminal nerve is very rare.[6] Clinical features of head and neck NMC are site dependent (retro-orbital pain, changes in hearing, other) sensorimotor deficits and some are entirely asymptomatic.[2, 6-8]

Microscopically these tumors are composed of an admixture of benign, mature neural, and muscular elements, with mature muscle fibers (most often skeletal muscle) inside the endoneurium.[5, 6] Skeletal muscle, with its peripherally located nuclei, is intensely immunoreactive for desmin and neural fibers dispersed among the muscle cells can be highlighted by neurofilament.[4] There is no necrosis, mitotic activity, neurons or ganglion cells.[2, 6, 8]

Additional reports and longer term follow-up of previously reported cases have led to the discovery of the association of NMC and the subsequent development of aggressive fibromatosis.[5, 9, 10] In one series of patients with NMC with adequate clinical follow up showed that 80% of the patients developed a desmoid-like fibromatosis in the soft tissues surrounding the NMC.[9, 10] It is possible that injury to the NMC (resection, biopsy, etc) stimulates the development of NMC-fibromatosis. The majority of desmoid-type fibromatoses are known to contain exon 3 *CTNNB1* mutations, and it has been recently shown that many NMC-fibromatosis, and in some cases NMC's, also have *CTNNB1* mutations.[5] This shared abnormality may be a key in greater understanding of their collective pathogenesis.

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## CASE 7

### DIAGNOSIS: ADENOID CYSTIC CARCINOMA, SOLID PATTERN OF GROWTH WITH AREAS OF HIGH-GRADE TRANSFORMATION

Adenoid cystic carcinoma (AdCC) is a morphologically bland but highly infiltrative and aggressive biphasic basaloid tumor whose clinical, pathologic features and relentless clinical course are well characterized.[1] A significant advance in the understanding of ACC came with the discovery and characterization of MYB and activation of its downstream targets in this tumor, specifically, an MYB-NFIB translocation t(6;9).[1, 2]

Microscopically, AdCC consists of an infiltrative proliferation of luminal ducts and abluminal myoepithelial cells arranged in tubular, cribriform or solid growth patterns. Individual neoplasms may have one dominant growth pattern, but most characteristically are composed of multiple patterns. Perineural invasion is almost invariably present with adequate sampling.[1] AdCC is generally resistant to presence of squamous/squamoid differentiation may be seen in areas of high grade transformation (HGT).[3, 4] Distinguishing solid growth from HGT can be difficult and/or require evaluation of multiple tumor sections and possibly evaluation of the tumor immunophenotype. Unique light microscopic features of HGT include micropapillary growth, squamoid features and fibrocellular desmoplasia of the stroma. Nonetheless, there is still morphologic overlap between solid conventional AdCC and AdCC-HGT and when seen together, the transition from solid conventional to AdCC-HGT is often gradual.[4] (SEE TABLE 1).

Table 1*	AdCC - Solid Pattern	AdCC - HGT
Chromatin	Dark homogeneous	Vesicular or heterogeneously dispersed
Nuclear membranes	Delicate	Thickened or irregular
Nucleoli	Present but indistinct	Prominent, central
Nuclear size	At most twice the size of grade I-II nuclei	At least 2-3x size of grade I-II
Cytoplasm	Scant to nearly absent	Scant to moderate
Grwoth	Solid nests, rarely spanning more than a 40hpf	Solid confluent nests to sheets often filling a 40hpf
Stroma	Paucicellular myxoid or hyaline	Fibrocellular desmoplastic
Comedonecrosis	Focally present, usually punctate	Often present, punctate to large zones
Microcalcifications	Rarely present	Often present

Unique features		Micropapillae, squamoid areas
Abluminal cell layer presence by immunohistochemistry	Present and complete	Incomplete and at least focally absent
Mitoses	Generally <10 hpf	Usually >10 hpf
Ki67	<50%	>50%
P53 overexpression (reactivity in >50% cells)	Rare	Common

- Adapted from Seethala et al.,[4]

Classical AdCC shows a slow but relentless progression. Five year survival is as high as 90% but 15 year survival is less than 70% and this decreases sharply afterward. Factors that influence survival include: growth pattern, node status, tumor stage and tumor site are commonly accepted prognosticators. In general, solid growth of more than 30% correlates with adverse outcome.[1] Early reports suggested AdCC-HGT to be a rapidly aggressive disease, even more so than solid AdCC.[4] More recently, this hypothesis has been challenged, however the low number of cases makes it difficult to study this disease.[3, 5] In classic AdCC the risk for regional spread is low (5-20%), and more commonly seen in solid growth and HGT. Approximately 50% of patients with AdCC show distant metastasis to lungs, followed by bone, liver and brain.[6]

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## CASE 8

### Diagnosis: p16 POSITIVE OROPHARYNGEAL SQUAMOUS CELL CARCINOMAS (OPSCCs)

Human papillomavirus (HPV) has been linked to the pathogenesis of squamous cell carcinoma (SCC) since the 1970s and, in 1995, it was recognized by the International Agency for Research on Cancer (IARC) that high-risk HPV types 16 and 18 were carcinogenic in humans.

High-risk human papillomavirus (HPV) is an established cause of head and neck carcinomas arising in the oropharynx and account for up to 80% of cases. About 18,226 (70%) people in the United States develop these cancers each year. This increasing incidence of HPV-positive OPSCCs perhaps results from increased oral sex, risky sexual behavior and oral HPV exposure over sustained period. HPV-positive OPSCCs have risk factors related to sexual behavior unlike HPV-negative one that are strongly associated with tobacco and alcohol use.

HPV-related carcinoma of the oropharynx predominates in men and the reasons remain unclear, more diagnosed in patients in their 40s through 60s. Furthermore, HPV positivity is associated with improved clinical outcomes.

Several studies on HPV-related squamous cell carcinomas of the oropharynx has provided new insights into HPV-related tumorigenesis and improved methods for HPV detection. One example is p53 and Retinoblastoma pathways inactivated by the viral oncoprotein induces overexpression of p16, such that immunohistochemical detection of p16 serves as a reliable surrogate marker for high risk HPV in oropharyngeal cancers. A significant issue with p16 IHC is that, until recently, there has been no consensus on the definition of a positive p16 IHC result. It has been recognized for decades that there should be extensive overexpression of p16 for it to suitably be a surrogate of high-risk HPV, but how extensive has been debatable.

The frequent detection of human papillomavirus (HPV) has generally evoked “guilt by association”, but the mere detection of HPV in sinonasal cancers has not proven an active role in carcinogenesis.

It has been proposed that this preferential targeting of the oropharynx may reflect the biological interaction between HPV and the lymphoepithelium (i.e. reticulated epithelium) lining the tonsillar crypts, where strong expression of PD-L1 results in a diminished cytotoxic T-cell response to viral antigens and potentially creates an ‘immune-privileged’ site for viral infection and persistence.

HPV-positive OPSCCs consistently arise from the tonsillar crypts, and they are not associated with keratinizing dysplasia of the surface epithelium. Most HPV-positive OPSCCs have a distinct non-keratinizing morphology. Non-keratinizing SCCs typically consist of large, pushing-bordered, or lobular architecture of nests of tumor cells with little or no discernible stromal reaction.

The morphologic spectrum of HPV-positive OPSCC includes basaloid and papillary SCC, adenosquamous, and sarcomatoid (or spindle cell) carcinomas. It also includes, as recently described in small patient series, the presence of ciliated tumor cells “ciliated adenosquamous carcinoma”. Although the number of reported cases of these variant forms is limited.

Standard treatment options for stage I and stage II oropharyngeal cancer includes radiation therapy using standard fractionation and surgery. For stage III and IV surgery and postoperative radiation therapy (PORT) with or without chemotherapy for patients with advanced disease. Radiation therapy

using altered fractionation as well as concurrent chemoradiation therapy and neo-adjuvant radiation therapy may sometimes remain the treatment of choice.

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#### CASE 9

##### **Diagnosis: P16 POSITIVE ADENOID CYSTIC CARCINOMA-LIKE MULTIPHENOTYPIC SINONASAL CARCINOMA (HMSC)**

Carcinomas of the sinonasal tract affect approximately 0.5 to 1.0 patients per 100,000 per year. High-risk types of human papillomavirus (HPV) are now well established as major etiologic factors of head and neck carcinoma but has not proven an active role in carcinogenesis in sinonasal tract.

Bishop et al. established that the 21% of sinonasal carcinomas are associated with HPV infection by using both p16 immunohistochemistry and HPV in situ hybridization. p16 is a useful immunohistochemical screen because all HMSCs are diffusely positive, but a definitive diagnosis requires subsequent HPV-specific testing.

One unique entity that does not have a counterpart in the oropharynx is HMSC a form of HPV-related carcinoma with features of a salivary tumor-like appearance with myoepithelial and ductal cells (previously known as HPV-related carcinoma with adenoid cystic carcinoma-like features) is very rare tumor restricted to the sinonasal tract of which few cases are reported. Most common HPV type associated with this carcinoma is HPV type 33, being detected in 68% of cases; other uncommon HPV types reported in this tumor are 35 (6% of cases), 56, 16, 52 and 26 No known prognostic factor for HMSC.

The age of patients ranged from 28 to 90 years old with women more affected than men. No specific race predisposition or definite link to cigarette smoking is established.

Common presenting symptoms include nasal obstruction, epistaxis and nasal discharge. The tumor most frequently arises in the nasal cavity, but may also occur in the paranasal sinuses, including maxillary sinus, ethmoid sinus, sphenoid sinus and frontal sinus.

HPV viral oncoprotein E7 deactivate tumor suppressor, result in overexpression of p16 protein that serves as a surrogate marker for transcriptionally active HPV infection

Microscopically, the carcinomas consist of highly cellular proliferations of basophilic cells. The most common architectural pattern according to several study was solid, with large lobules and sheets separated by thin fibrous bands. Microcystic spaces filled with mucoid material. The least common reported pattern was tubular. Areas of cellular tumor necrosis, and the mitotic rates ranged from 3 to 150 per 10 high power fields was also reported. Bone & perineural invasion was identified in few cases.

Importantly, HMSC does not always closely resemble adenoid cystic carcinoma, and can resemble squamous cell carcinoma or other salivary gland tumors and should be separated from sinonasal adenoid cystic carcinoma. The above diagnosis should be considered for any unusual-appearing carcinoma, especially if it resembles a salivary gland tumor.

To date, no perfect or consensus treatment for HMSC has been established. Most patients are surgically treated with or without adjuvant chemotherapy or radiotherapy. In a recent case series with a total of 49 cases, it has been stated that about 36% of the patients developed local recurrences, and (5%) developed distant metastases in the lung and finger following surgery. This situation of distant metastases had not been previously reported. Although 43% of the patients in that series presented with advanced tumor stage, none of them developed lymph node metastasis or died of their disease, which may indicate a relatively indolent clinical behavior compared with other sinonasal carcinomas.

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## Case 10.

### **EPITHELIOID (AGGRESSIVE) OSTEOLASTOMA**

The term aggressive osteoblastoma (AO) is assigned to a primary neoplasm of bone that straddles the borderline between conventional osteoblastoma (CO) and low-grade osteosarcoma. These lesions tend to exhibit brisk recurrence but do not metastasize. AO are microscopically characterized by the presence of epithelioid osteoblasts. The term AO was introduced in 1984 by Dorfman and Weiss. Other names such as pseudo-malignant osteoblastoma and malignant osteoblastoma have also been proposed. AO is a very rare neoplasm that is purported to have clinic-pathologic features that set it apart from CO. This entity continues to remain controversial and often creates difficulty in distinguishing from a low-grade osteosarcoma.

Osteoblastoma account for less than 1% of primary bone tumors. A slight male predilection has been reported. These lesions have been reported to occur virtually in any part of the skeletal system but commonly affect the spine, long bones and sacrum. The maxillofacial region is affected in only approximately 11% of the patients with the mandible being the most common site. CO is more common in the first two decades of life though a wide age range is noted. Due to the relative rarity, the incidence and distribution of AO is not established. AO is generally seen in an older age group than CO.

Radiographically, CO presents with a round to oval radiolucent area infrequently demarcated by a sclerotic margin. Many lesions produce with a central nidus of sclerotic bone surrounded by a radiolucent halo similar to osteoid osteoma. The lesions are sharply marginated and have a peripheral rind of sclerotic bone. CO is rarely larger than 4 cm whereas AO have been reported to be greater than 4 cm in size. In addition, cortical expansion, permeation into surrounding bone, movement of teeth and resorption of roots of teeth in the region have all been reported with AO. Clinically, AO exhibits aggressive behavior and is able to extend into adjacent tissues. A recurrence rate ranging from 10-20% has been reported but no metastases described.

Importantly, the histomorphology of AO is distinctive and has overlapping features with low-grade osteosarcoma. Some authors advocate that lesions described as AO are, in fact, well-differentiated osteosarcoma resembling osteoblastoma. The diagnostic evaluation is based on the histologic features and the clinical behavior of the lesion. Microscopically, large epithelioid osteoblasts, exhibiting abundant eosinophilic cytoplasm twice the size of conventional osteoblasts are seen distributed in a highly vascular stroma interspersed by varying numbers of dilated capillaries (telangiectasia). Abundant osteoid is noted and has been described as spiculated "blue bone". The neoplastic cells either rim the osteoid as in conventional osteoblastoma or arrange themselves in sheets and clusters devoid of matrix. Often interspersed among sheets of tumor cells are varying amounts of homogeneous, pale-staining extra-cellular eosinophilic material which closely mimic amyloid (negative for Congo red). Cellular and nuclear pleomorphism is present. Osteoclastic giant cells often seen in osteoblastoma are usually not present in the aggressive epithelioid variant. Mitoses are usually rare and if seen tend to be normal appearing.

The histologic differential diagnosis for AO includes low-grade osteosarcoma. The presence of large numbers of pleomorphic epithelioid osteoblasts with abundant osteoid. Careful examination of the tumor margins of AO and its interaction with normal cortical bone along with its clinical presentation is paramount in distinction from a low-grade malignancy. Some authors believe that the chief features

that separate osteosarcoma from osteoblastoma is the lack of tumor maturation at the margins of osteosarcoma, with permeation of tumor into adjacent tissues, in contrast to maturation at the margins and lack of permeation into the adjacent bone in osteoblastoma. To confuse matters further, and osteoblastoma-like osteosarcoma has also been reported with incidences of distant metastases, local recurrence and death. Though, a malignant transformation rate of CO is estimated to be less than 1%.

Immunohistochemical stains are usually not very helpful since markers of osteoblastic differentiation are positive in both osteoblastoma as well as low-grade osteosarcoma. These include SATB2 which is diffusely positive in both. MDM2 another immunohistochemical marker often positive in osteosarcoma due to its interaction with p53 tumor suppressor gene has been reported to be positive in osteoblastoma. In our case, SATB2 was diffusely and strongly reactive for the lesional cells. Scattered MDM2 positive (nuclear) tumor cells were also seen within the specimen.

Wherever the location, most case reports and studies have reported AO should be treated with marginal resection to avoid recurrences. Recurrence usually occurs when curettage or incomplete excision is performed. Our patient was treated with marginal resection of the mandible.

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