Introduction

Glandular lesions/neoplasms of the sinonasal tract include nonneoplastic lesions (e.g., seromucinous hyperplasia, hamartomas), benign neoplasms (e.g., pleomorphic adenomas, others) and malignant neoplasms (e.g., adenocarcinomas). In limited biopsies such glandular lesions may histologically appear similar potentially resulting in an erroneous diagnosis and the potential for unwarranted management. This talk will focus on the diagnostic features and differentiating findings among this group of sinonasal glandular proliferations with an emphasis on sinonasal seromucinous hamartoma and sinonasal low-grade adenocarcinoma.

Sinonasal Hamartomas

Sinonasal hamartomas are considered uncommon lesions. The majority of hamartomas of this region is of the pure epithelial type and includes respiratory epithelial adenomatoid hamartoma and seromucinous hamartoma. Other less common types of hamartomas are the mesenchymal hamartomas or mixed epithelial-mesenchymal hamartomas.

Seromucinous Hamartoma (SH)

Seromucinous hamartoma of the sinonasal tract is a benign acquired nonneoplastic overgrowth of indigenous glands of the sinonasal tract, and rarely of the nasopharynx, arising from submucosally situated seromucinous glands. SH were initially described by Baille and Batsakis [1] in a case report of a patient with a nasopharyngeal lesion. Subsequent to that description, there have been a number of other case reports but only recently was SH the subject of larger studies, including 7 cases reported by Weinreb et al [2] and 5 cases reported by Ambrosini-Spaltro et al.[3] To date, there are less than 25 cases of SH identified in the world literature.[1-7]

Clinical

SH most commonly occurs as an incidental finding seen in surgical material from patients removed for clinical diagnoses such as chronic sinusitis and/or sinonasal inflammatory polyps. Symptomatic patients may present with nasal obstruction and epistaxis. There is a slight male predilection and SH occur over a wide age range including 2nd decade to 9th decade of life. The most common site of occurrence is the posterior nasal septum although SH may occur in the lateral nasal wall, paranasal sinuses and nasopharynx. Although general limited in extent, SH may extend into adjacent sinuses (e.g., maxillary, ethmoid). There are no known etiologic factors although some patients with SH have been reported in association with chronic sinusitis, inflammatory polyps, rheumatoid arthritis and Parkinson disease. Radiographically, SHs may appear as polypoid lesion without evidence of aggressive growth such as bone destruction or neuropathies.

Pathology

SH are polypoid to exophytic appearing lesions measuring from 6mm to 4 cm in greatest
dimension. Histologically, SH are covered by benign ciliated respiratory epithelium that may show squamous metaplasia and often have an associated hypocellular edematous, myxoid and/or fibrous stroma similar to that seen in sinonasal inflammatory polyps. The characteristic finding is the presence of a submucosal epithelial proliferation of small glands, serous acini and tubules growing in clusters and lobules although haphazard arrangement with larger glands and cysts are seen. In some cases the serous glands may be densely packed with a back-to-back appearance that may resemble a cribriform pattern of growth. The glands are lined by low cuboidal to flat epithelium cells with round to oval nuclei and a variable amount of basophilic to eosinophilic to clear appearing cytoplasm. There is an absence of significant nuclear pleomorphism, increased mitotic activity and necrosis. Invagination of the surface respiratory epithelium may be seen with at least focal merging with the glandular proliferation. Periglandular hyalinization may also be present. The glands vary in appearance from appear round to oval to angulated to branching and stellate containing luminal mucin material. SHs lack a significant mucinous cell component although focal mucinous change may be found. Residual seromucinous glands with retention of their lobular architecture and haphazard growth of glands represent important findings in SH that allow for differentiation from sinonasal low-grade adenocarcinoma. A mixed chronic inflammatory cell infiltrate comprised of mature lymphocytes and plasma cells can be seen but a significant population of eosinophils is not typically present.

**Immunohistochemistry**

Surface epithelium and the seromucinous glands are reactive for cytokeratins, including CK7, CK17, CK19 and high molecular weight cytokeratin (HMWK) but negative for CK14 and CK20. The surface respiratory epithelium shows p63 positive basal cells but the seromucinous glands are negative for p63.[1,3,4] In addition, calponin and muscle specific actin are negative in both the surface respiratory epithelium and the seromucinous glands. Fleming et al [7] reported a case of SH showing p63, calponin and actin staining indicating that not all SHs lack p63 reactivity. S100 protein staining is limited to the seromucinous glands. Collagen type IV and laminin staining is present around the glandular proliferation. Ki67 (MIB1) staining is either absent or shows a very low proliferation rate (1-2%).

**Molecular Findings**

Most authorities view SH as a nonneoplastic proliferation. However, Ozolek and Hunt [8] evaluated the molecular profile of sinonasal hamartoma, sinonasal adenocarcinomas and chronic sinusitis. These authors found a fractional allelic loss (FAL) of 31% in hamartomas, 64% in sinonasal adenocarcinoma and 2% in chronic sinusitis. The authors indicated that based on the molecular profile of hamartomas which would be considered unusually high for a non-neoplastic entity that the appreciable allelic loss within hamartomas suggests the possibility that they may be a benign neoplasm rather than a hamartoma. Ambrosini-Spaltro et al [3] performed DNA mutation analysis on SH that showed a higher
mutation rate in comparison to normal seromucinous glands which exhibited a lower mutation frequency (0.83%) supporting SH as representing a benign process although no comments relative to their neoplastic nature was offered. These authors did state the similarities of SH to microglandular adenosis of the breast.

**Treatment and Prognosis**

The treatment for SH include simple but complete surgical resection which is curative with no reported recurrences over extended periods of time.

**Differential Diagnosis**

The differential diagnosis for SH includes other benign lesions such as respiratory epithelial adenomatoid hamartoma (REAH) and Schneiderian papillomas as well as sinonasal adenocarcinomas. 

**REAH**

REAH is a benign acquired nonneoplastic overgrowth of indigenous glands of the nasal cavity, paranasal sinuses and nasopharynx arising from the surface epithelium and devoid of ectodermal neuroectodermal, and/or mesodermal elements.[9]

REAHs are typically polypoid or exophytic lesions with a rubbery consistency, tan-white to red-brown appearance measuring up to 6 cm in greatest dimension. The histopathologic changes are dominated by the presence of a glandular proliferation composed of widely-spaced, small to medium-sized glands separated by stromal tissue. In areas the glands are seen arising in direct continuity with the surface epithelium, which invaginate downward into the submucosa. The glands are round to oval composed of multilayered ciliated respiratory epithelium often with admixed mucin-secreting (goblet) cells. A characteristic finding is the presence of stromal hyalinization with envelopment of glands by a thick, eosinophilic basement membrane. Atrophic glandular alterations may be present in which the glands are lined by a single layer of flattened to cuboidal-appearing epithelium. Small reactive appearing seromucinous glands can be seen. The stroma is edematous or fibrous containing a mixed chronic inflammatory cell infiltrate. In addition to the glandular proliferation, other findings that can be found in association with the REAHs include: alterations of inflammatory sinonasal polyps; hyperplasia and/or squamous metaplasia of the surface epithelium unrelated to the adenomatoid proliferation; osseous metaplasia; rare association with inverted type Schneiderian papilloma, and rare association with a solitary fibrous tumor.[9] Histologic features of REAH can be present in any case of SH suggesting that these hamartomas represent a spectrum of lesions rather than 2 distinct lesion types.

Immunohistochemical staining of REAH show the glands to be reactive for CK7 but not for CK20 and CDX2. Further, p63 and 34βE12 staining of basal (myoepithelial) cells is present.[10]

REAH are benign cured by conservative excision with no recurrences, metastases and/or associated deaths.

**Schneiderian Papillomas**
Superficial biopsies of Schneiderian papilloma, cylindrical cell type may be confused with SH and sinonasal low-grade adenocarcinoma. These papillomas are characterized by the presence of a multilayered epithelial proliferation composed of columnar cells with abundant eosinophilic and granular cytoplasm. The nuclei vary from vesicular to hyperchromatic; nucleoli are usually indistinct. The outer surface of the epithelial proliferation may demonstrate cilia. Intraepithelial mucin cysts, often containing polymorphonuclear leukocytes, are seen; cysts are not identified in the submucosa. The stromal component varies from myxoid to fibrous with admixed chronic inflammatory cells and variable vascularity. The intraepithelial mucocytes show intracytoplasmic mucin positive material (mucicarmine positive; diastase-resistant, PAS-positive).

Sinonasal Adenocarcinomas

Sinonasal adenocarcinomas are a heterogeneous group of neoplasms that include salivary gland types, intestinal types and non-intestinal, non-salivary gland types. A brief discussion of all 3 types of sinonasal adenocarcinomas are presented here but the key adenocarcinoma type to differentiate from SH is a sinonasal low-grade adenocarcinoma, non-salivary gland, non-intestinal type.

Salivary Gland Type Adenocarcinomas

Malignant minor salivary gland neoplasms of the sinonasal tract are uncommon. The most common type of malignant minor salivary gland neoplasms seen in the sinonasal tract is the adenoid cystic carcinoma. The histologic features of sinonasal adenoid cystic carcinoma is identical to that adenoid cystic carcinoma originating in major and other minor salivary gland sites. Less commonly, other types of malignant minor salivary gland neoplasms may occur in the sinonasal tract, including (but not limited to) mucocystic carcinoma and epithelial-myoeplithelial carcinoma. There are no known etiologic factors associated with the development of sinonasal malignant minor salivary gland neoplasms, including occupational and environmental exposures.

Intestinal type Adenocarcinomas

The intestinal-type adenocarcinomas (ITACs) of the sinonasal tract are malignant epithelial glandular tumors of the sinonasal tract that histologically resemble intestinal adenocarcinoma. ITACs occur over a wide age range but are most common in the fifth to seventh decades of life. ITACs most frequently involve the ethmoid sinus followed by the nasal cavity (inferior and middle turbinates) and maxillary sinus; however, ITAC may arise anywhere in the sinonasal tract. Early symptoms tend to be non-specific and vary from nasal stuffiness to obstruction that, with persistence, may be associated with epistaxis, prompting further clinical evaluation. Due to the delay in diagnosis, tumors may reach a large size with extensive invasion at the time of presentation. Etiologic factors associated with the development of ITAC include exposure to hardwood dust, leather and softwood; increased incidences of adenocarcinoma are seen in woodworkers and workers in the shoe and furniture industries. Sporadic
ITACs unassociated with occupational exposure occur and tend to affect women more than men, with most tumors involving the maxillary antrum.

Histologically, Barnes [11] divided these tumors into 5 categories, including: papillary; colonic; solid; mucinous; and mixed. An alternative classification scheme proposed by Kleinsasser and Schroeder [12] divided ITACs into four categories, including: papillary tubular cylinder (PTCC) types I-III (I = well-differentiated, II = moderately-differentiated and III = poorly-differentiated); alveolar goblet type; signet-ring type; and transitional type. Either classification is acceptable, but for simplicity the Barnes classification is preferred. The most common histologic types seen in association with woodworkers as well as in sporadically occurring cases are the papillary and colonic types. Irrespective of the histologic type, ITAC histologically simulate normal intestinal mucosa and may include villi, Paneth cells, enterochromaffin cells and muscularis mucosa. Stains for epithelial mucins are positive including intracytoplasmic and extracellular mucicarminophilia. In addition to immunoreactivity for pancytokeratins and other epithelial markers ITACs are immunoreactive for CK20, CDX-2 and villin.

The treatment for ITAC is complete surgical excision. Radiotherapy may be utilized for extensive disease or for higher grade neoplasms. All the intestinal-type adenocarcinomas are considered as potentially aggressive, lethal tumors. Metastasis to cervical lymph nodes and spread to distant sites are infrequent occurring in about 10% and 20%, respectively. The 5-year cumulative survival rate is around 40%, with most deaths occurring within 3 years. Death results from uncontrollable local or regional disease with extension and invasion of vital structures and/or metastatic disease. ITACs are generally locally aggressive tumors with frequent local failure (about 50%); since most patients present with advanced local disease, clinical staging generally has no relevant prognostic significance. The histologic subtype has been identified as indicative of clinical behavior, with the papillary type (grade I) lesions behaving more indolently than the other variants. There is no difference in behavior between ITAC occurring in occupational exposed individuals and sporadically occurring ITAC.

**Non-Salivary, Non-Intestinal Types Adenocarcinomas**

The sinonasal tract non-salivary gland, non-intestinal adenocarcinomas are malignant glandular neoplasms that do not demonstrate histopathologic features that would allow classification as a distinct minor salivary gland neoplasm or demonstrate features allowing for classification as a sinonasal intestinal type of adenocarcinoma. These adenocarcinomas include low-grade and high-grade types. The low-grade adenocarcinoma may be confused with seromucinous hamartoma.

**Low-Grade Adenocarcinoma**

Sinonasal low-grade adenocarcinomas predominantly occur in adults but have been identified over a wide age range from 9 to 80 years. For the low-grade adenocarcinomas there is a slight male predominance; average age at presentation of 53 years. This tumor type predilects to the ethmoid sinus (to
a lesser extent as compared with the “intestinal” type) but may occur anywhere in the sinonasal tract, including the nasal cavity and maxillary sinus.[13-15] Typically, these neoplasms are incidental findings identified in resection specimens in patients presenting with nasal obstruction clinically thought to have inflammatory polyps or chronic sinusitis. Pain is an infrequent feature. There are no known occupational or environmental factors associated with the non-salivary gland, non-intestinal type adenocarcinomas. Jo et al [xx] reported that some of their cases of low-grade adenocarcinomas were associated with REAHs prompting these authors to implicated REAHs as a precursor lesion for at least a subset of sinonasal low-grade adenocarcinomas.[16]

Whether low- or high-grade may be seen entirely within the submucosa often without surface involvement but transitional areas from normal surface ciliated respiratory epithelium (with or without squamous metaplasia) to carcinoma may be identified.[13] The low-grade adenocarcinomas have a glandular or papillary growth and may be circumscribed but are unencapsulated tumors. These neoplasms are characterized by the presence of numerous uniform small glands or acini often with a back-to-back growth pattern without an intervening stroma, as well as papillary projections, epithelial tufting and trabeculae; occasionally, large, irregular cystic spaces can be seen. The glands are lined by a single layer of nonciliated, cuboidal to columnar cells with uniform, round nuclei which may be limited to the basal aspect of the cell or may demonstrate stratification with loss of nuclear polarity and an eosinophilic cytoplasm. Cellular pleomorphism is mild to moderate and occasional mitotic figures are seen but atypical mitoses and necrosis are absent. Despite the relatively bland histology, the complexity of growth, absence of two cell layers, absence of encapsulation and presence of invasion into the submucosa confer a diagnosis of adenocarcinoma. Histologic variants include papillary, tubulopapillary, clear cell and oncocytic adenocarcinomas. Multiple morphologic patterns may be seen in any one neoplasm.

Immunohistochemical staining shows reactivity for cytokeratins (AE1/AE3, CAM5.2, CK7, CK19) and S100 protein but absence of CK20, CDX2, MUC2, villin and p63.[17]

The treatment for all the histologic variants of non-intestinal, non-salivary gland sinonasal adenocarcinomas is complete surgical excision generally via a lateral rhinotomy; depending on the extent and histology of the neoplasm the surgery varies from local excision to more radical procedures (maxillectomy, ethmoidectomy and additional extenterations). Radiotherapy may be utilized for extensive disease or for higher grade neoplasms. The prognosis for sinonasal low-grade adenocarcinomas is good with reported 3 year survival rates of 70-89%.[12,13-18] Death due to disease is rare but occurs and is the results of uncontrollable local invasion. High-grade adenocarcinomas have a dismal prognosis with 3 year survival rates of approximately 20%.

Conclusions

The spectrum of glandular lesions of the sinonasal tract is broad to include noneoplastic lesions
(heretofore designated as hyperplasias and hamartomas) and neoplasms. The latter primarily include the heterogeneous group of adenocarcinomas classified as salivary gland types, intestinal types and non-salivary gland, non-intestinal types. There are overlapping clinical and to some degree histologic and immunohistochemical features shared by seromucinous hamartoma (SH) and sinonasal low-grade adenocarcinomas of the non-salivary gland, non-intestinal types that may result in misdiagnosis and inappropriate management. Criteria assisting in diagnosing SH and differentiating it from low-grade adenocarcinoma include retention of lobular architecture and haphazard growth of glands. Controversial issues relative to sinonasal glandular lesions include whether sinonasal hamartomas represent a nonneoplastic proliferation or whether these lesions are more appropriately classified as adenomas based on the levels of functional allelic losses between sinonasal polyps and adenocarcinomas. In either event, they are benign and cured by simple excision.
References