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**Low Grade Glandular Lesions of the Sinonasal Tract: A Focused
Review**

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Brief points:

- **Respiratory epithelial adenomatoid hamartoma (REAH) is a proliferation of invaginated back to back respiratory lined glands that may mimic inverted papilloma or low grade adenocarcinoma.**
- **Seromucinous hamartoma is a low grade tubular lesion with similar clinicopathologic findings to REAH but with smaller unilayered glands.**
- **Both REAH and seromucinous hamartoma show minimal deviation from normal sinonasal elements except the density of the glands.**
- **Low grade non-intestinal salivary adenocarcinomas are a diverse group of neoplasms and may occasionally be seen with a REAH component.**
- **The relationship between these lesions has yet to be clarified.**

Abstract:

The sinonasal tract is a complex anatomic site with an exhaustive list of possible diagnoses. While most biopsies or resections encountered routinely consist of common diagnoses such as inflammatory polyps and papillomas, occasional cases are more difficult, and separating reactive or benign from malignancy can be challenging. One of the most poorly understood and daunting categories is low grade glandular or tubular proliferations, particularly on small biopsies. Possible diagnoses such as reactive lesions, respiratory epithelial adenomatoid hamartoma (REAH), seromucinous (glandular) hamartoma (SH) and low grade sinonasal adenocarcinomas (LGSNAC) must be entertained. REAH is composed of respiratory epithelial lined submucosal glands with variable connection to the surface and periglandular hyalinization. SH is a tubular proliferation reminiscent of normal serous glands which may be associated with REAH.

LGSNAC is a diverse group of bland tubular and/or papillary tumors, which have a recurrence potential but an as yet uncertain potential for metastasis or mortality. The management for these lesions can be vastly different and conservative management is preferable, making this distinction more than academic. However, complicating this category are controversies surrounding their nature as reactive lesions versus neoplasms, the histologic and immunohistochemical overlap, and possible precursor relationships between some of them.

Introduction:

The sinonasal tract is home to a dizzying array of reactive, benign neoplastic and malignant entities and separating these can be difficult owing to the limited nature of biopsies from this site that are encountered in surgical pathology practice. Most of these consist of inflammatory polyps, papillomas and squamous cell carcinomas (1). Other diagnoses such as salivary type tumors, olfactory neuroblastomas and poorly differentiated carcinomas may occasionally be seen but are familiar to most surgical pathologists. The diagnosis becomes more complicated when a biopsy or polypectomy yields a low grade glandular proliferation. In this circumstance, the differential diagnosis includes reactive proliferations, respiratory epithelial adenomatoid hamartoma, glandular (seromucinous) hamartoma and low grade sinonasal adenocarcinomas. Immunohistochemistry does not offer much help in this differential diagnosis, save the exclusion of intestinal type adenocarcinomas, most of which do not represent pure low grade tubular lesions (2). This review will focus on low grade glandular lesions of the

sinonasal tract, their typical morphologic appearance and overlap, and controversies regarding their neoplastic nature and biologic potential.

Discussion:

Respiratory Epithelial Adenomatoid Hamartoma:

Respiratory epithelial adenomatoid hamartoma (REAH) was first described by Wenig and Heffner in 1995 as a benign overgrowth of submucosal ciliated respiratory lined glands forming a polypoid mass lesion (3). It may arise in any part of the nasal tract, although a predilection for the posterior nasal septum has been noted, unlike typical inflammatory polyps or sinonasal adenocarcinomas (4). The overwhelming majority of cases occur in males and a wide age range has been described (3, 4). The most common presentation is with unilateral obstructive symptoms or epistaxis and these may arise over the course of months or even years. To date, there have been no examples of REAH with aggressive behavior or convincing examples of recurrence after complete excision (4); although recurrence of associated nasal inflammatory polyps has been noted (5).

The glands typically are back-to-back with minimal intervening stroma, a connection to the surface epithelium and periglandular hyalinization (figure 1a) (3). Some cases show so-called atrophy, where the epithelium is attenuated to a single flattened layer with a collapsed appearance (figure 1b). A minority of cases contain mucinous cells and distension of lumina by mucin and these can dominate an occasional lesion, in our

experience (figure 2). Some cases may show focal hyperplasia of the native seromucous glands adjacent to the respiratory glands (3). Whether this is truly a reaction to the REAH or part of the process has been debated (3, 5). Although the epithelium in REAH is described as multilayered, it is perhaps more appropriate to define it as pseudostratified columnar epithelium +/- goblet cells. This differentiates it from its principle differential diagnosis, namely inverted papilloma, which shows a similar back-to-back nested architecture and connection to the surface, but has true multilayering by “transitional type” cells. Many cases of inverted papilloma may show well developed multilayering only focally, so the presence of inverted papilloma-like areas should trump REAH-like areas when making a diagnosis. REAH has been reported to be positive for CK7 and negative for CK20, CDX2 and S100. It shows a p63 and 34 β E12 positive basal layer (6) but there is little role for immunohistochemistry in most cases, which can readily be diagnosed with routine stains.

The initial use of the term hamartoma may have reflected lesional composition by cell types normally seen in the sinonasal tract and the belief that REAHs were non-neoplastic (3). Examples of so-called COREAH (chondro-osseous REAH) have been described, where either chondroid or bone are present within a REAH (7, 8), which still could be in keeping with a hamartomatous process given the normal appearance of these structures in the nasal cavity. The chondro-osseous components could alternatively be normal structures entrapped by the REAH rather than a part of the proliferation. The designation of hamartoma in the strictest sense implies a potential congenital origin as a disorganization of normal tissues. Of note, we have seen a case of bilateral REAH in a 10 day old infant,

which may serve to support this concept. Most REAH's however occur in adult populations and are likely acquired.

Although an association with an occasional inverted papilloma and solitary fibrous tumor was originally described (3), there are no precursors or etiologic factors that would explain the growth of REAH. Inflammatory nasal polyposis is often noted adjacent to or preceding REAH, however and a reactive process may be at play. Many cases of normal sinonasal mucosa or inflammatory polyps in our experience can show focal groups of invaginated respiratory glands and even thickened basement membrane-like material, but do not qualify as REAH. We have also seen cases of REAH in association with olfactory neuroblastoma, osteoma post basal skull fracture or other seemingly unrelated processes, suggesting that REAH may occur as a local reaction to a mass. Ozolek et al on the other hand described loss of heterozygosity rates (fractional allelic losses) for REAH that are intermediate between inflamed mucosa and sinonasal adenocarcinoma and suggested that it may represent a benign neoplasm (9). This would be in keeping with the finding of a neoplastic origin for many other so-called hamartomas in the body, such as angiomyolipoma of the kidney (10). Jo et al, have suggested that REAH and the related seromucinous hamartomas (see below), may be more accurately designated as "adenomas", reflecting this possible neoplastic nature (11). It cannot be discounted however that REAH may begin as an exuberant reactive process and acquire secondary genetic changes to render it a self sustaining clonal neoplasm. More molecular data are required to study this process further to fully explore its nature, particularly as some

authors (11) have attributed occasional adenocarcinomas to an origin in REAH (see later).

Seromucinous hamartoma:

Seromucinous hamartomas have been described in several case reports and small series (5, 12-15). They have been referred to as “serous hamartoma”, “glandular hamartoma” and “microglandular adenosis” (12, 13). These lesions, like REAH, arise mostly in the posterior nasal septum and nasopharynx (80%) although they have also been described in the lateral nasal wall (5). No cases have been described in sinuses to date. They present as polypoid masses with a wide age range (14 - 85) and a slight male predominance (3:2) and have a similar presentation (obstructive symptoms) to other benign sinonasal lesions (5).

Most of these lesions are made up of a lobular growth of small tubules with occasional irregularly shaped glands that are primarily composed of serous cells with eosinophilic cytoplasm (figure 3). They do not show the epithelial tufting, micropapillae, haphazard back-to-back growth or cribriforming that can be seen in sinonasal adenocarcinomas. Occasional cases show focal clear cell changes or PAS positive oncocytic granules. Mucinous cells are not a common feature despite the name “seromucinous hamartoma” which denotes the presumed seromucinous gland origin rather than the cell content. The nuclei are small and there is no appreciable mitotic activity or necrosis (figure 4). The

background stroma shows a variable mixed chronic inflammatory infiltrate, edema and fibrosis.

Most cases show at least focal REAH-like changes (figure 3-4). This may consist of isolated or prominent intermixed invaginated respiratory lined glands and cysts or even areas of classic REAH forming a “hybrid tumor” (5). In our series, three cases were noted to have periglandular hyalinization, a feature not previously appreciated. In one case this feature was seen around serous glands, but otherwise it is generally identified around invaginated respiratory glands, similar to REAH. Some of these REAH-like glands were noted to have the smaller serous glands “bud” from them, which suggests a common origin for the two parts of the lesion. This may imply a Schneiderian mucosal origin rather than seromucous gland origin. Seromucinous hamartomas typically stain for S100 and CK7 and are negative for CK20, similar to REAH. They show no myoepithelial layer with actin and calponin and also lack the p63 and 34 β E12 basal layer seen in REAH and the overlying respiratory epithelium (5, 13, 15). This may serve to simulate an invasive tumor, however an infiltrative pattern is not observed in seromucinous hamartomas. Where the serous glands bud from the REAH-like glands, the basal layer is abruptly lost and S100 positivity is similarly gained in the smaller serous glands (5).

Along with posterior nasal septal location, these findings were argued to represent a spectrum of change between seromucinous hamartomas and REAH with hybrid lesions in between, rather than distinct entities (5). It is possible that the seromucinous gland hyperplasia originally noted in the background of REAH by Wenig and Heffner

represents a part of the lesion rather than a secondary phenomenon (3). There have been no molecular data in seromucinous hamartoma to explore its relationship to REAH or to determine whether it represents a neoplasm rather than an exuberant reactive process.

Despite the similarities cited between REAH and seromucinous hamartoma, it should be noted that the typical features of both lesions can be seen focally in inflammatory polyps and even inflamed sinonasal mucosa. When these features become prominent enough to call a hamartoma or whether they represent early precursors is not currently understood. Their frequent occurrence in normal mucosa, however would lend credence to the hypothesis that hamartomas may begin as reactive lesions, whether or not they represent clonal neoplasms as Ozolek et al have suggested (6). It has also been my experience that these focal changes in inflamed or normal mucosa have inconsistent myoepithelial staining (actin, calponin) and that the lack of a myoepithelial layer is not unique to hamartomas and adenocarcinomas. In addition, the frequency of these findings in normal and inflamed sinonasal mucosa suggests that a diagnosis of REAH or seromucinous hamartoma requires large fragments of tissue or whole polypectomy specimens and that a diagnosis should not be made on small fragmented biopsies.

A chondro-osseous or other mesenchymal component has not been described thus far in seromucinous hamartoma, although we have seen a recent case in the lateral nasal wall that showed the serous glands within the gaps of otherwise undisturbed nasal bone. This could easily be misdiagnosed as bone invasion or an “osseous seromucinous hamartoma”. However, the presence of a lobular growth of the glands, inflammation, normal

appearance of the bone, and identification of normal seromucinous glands within these gaps is paramount in avoiding this misinterpretation.

Low grade sinonasal adenocarcinoma:

The most important tumors that require distinction from benign hamartomas are low grade tubular adenocarcinomas that can rarely arise in the sinonasal tract. Sinonasal adenocarcinomas are currently classified by the WHO into salivary type and non-salivary type (16). The former are essentially identical to their salivary counterparts with adenoid cystic carcinoma, basal cell adenocarcinoma and epithelial-myoepithelial carcinoma being the most similar due to their occasionally predominant tubular appearance. All of these contain well defined myoepithelial populations, which is a feature not seen in sinonasal hamartomas. These entities are generally readily distinguished from hamartomas and will not be discussed here.

The non-salivary group is composed of intestinal type and non-intestinal type adenocarcinomas, each of which can be low or high grade. Even within the low grade subset, intestinal type adenocarcinomas (ITAC) are considerably different looking than hamartomas as they often show more columnar cells, goblet or mucinous cells and may have papillary formations, cribriforming or solid patterns; findings that are not typical of sinonasal hamartomas (2, 5). They resemble intestinal epithelium in the normal, dysplastic and malignant states (16). They often arise in the ethmoid sinus, which represents an unusual location for sinonasal hamartoma and are associated with wood

dust and other occupational exposures (2, 16, 17). They are readily distinguished by their typical staining for CK20 and/or CDX2, a feature not seen in sinonasal hamartomas. However, we have seen an occasional case of low grade ITAC that has appeared deceptively bland and formed only small tubules with no complex cribriforming, papillary or solid formations and was only discovered upon immunohistochemical staining (figure 5a-b). This distinction is important as ITACs represent an aggressive group of tumors. For this reason, we stain all low grade tubular lesions with CK20 and CDX2.

Non-intestinal sinonasal adenocarcinomas are also separated into low and high grade categories, but are more poorly defined than ITAC, particularly in the high grade group (16). They are of presumed seromucous gland origin and have a variety of growth patterns and in some ways represent a diagnostic category of exclusion. Low grade sinonasal adenocarcinomas (LGSNAC) can arise anywhere in the sinonasal tract and occur over a wide age range (11, 16). Unlike in sinonasal hamartomas and ITAC's, there appears to be no gender predilection (11). They have no association with occupational exposures and no definitive precursors have been identified, although a possible evolution from REAH has been suggested for a small subset (11).

Histologically they typically show a combination of bland uniform tubules with small micropapillae in the form of epithelial tufts (figure 6) or larger but delicate papillae with fibrovascular cores (11, 16). The cells are small, bland and often show a columnar appearance with minimal atypia. Some cases may show microcysts filled with mucin (16,

18). Although invasion is difficult to identify in some cases, the exophytic papillary nature of many of the tumors or complex growth patterns including back-to-back growth, infiltrative appearance, fusion of tubules, trabeculae and lack of lobular growth differ from the more uniform architecture seen in hamartomas (11). That being said however, there is often inflamed stroma (as with hamartomas) and the hallmark signs of malignancy such as perineural invasion, lymphovascular invasion, mitotic figures and necrosis are generally absent (11, 16). This makes distinction from seromucinous hamartoma and even inflamed sinonasal mucosa difficult or impossible on small biopsies. LGSNACs are positive for CK7 and often S100. They are negative for CK20, MUC2 and CDX2 (11). Immunohistochemistry does not however, help in the distinction from hamartomas.

Jo et al reported a small group of LGSNACs which they believed were associated with REAH (11). Some of these were identical to other non-REAH associated SNACs described in the literature, while others were felt to have overlap with what we have called “seromucinous hamartoma” (5). The principle difference they cited was the focal fusion of glands in their LGSNACs and lack of the lobular growth pattern that was present in all of our seromucinous hamartomas.

Conclusions:

Low grade glandular lesions of the sinonasal tract are a diverse group with a great degree of overlap. On small biopsies they may not be distinguishable at all and save CK20 or

CDX2 positivity in low grade ITACs, there is minimal role for immunohistochemistry. Some cases represent REAH, which is a distinct clinicopathologic entity with a predilection for the posterior nasal septum. Others are obvious carcinomas with infiltrative features and a defined recurrence potential. The remainder are a nebulous group of bland tubular lesions, some of which have been considered hamartomas while others have been considered adenocarcinomas. An association with REAH has been ascribed to both. The fact that the nature of REAH (reactive, hamartomatous or adenomatous) isn't fully understood further complicates this group. No REAH-associated lesion that has been called seromucinous hamartoma or LGSNAC has recurred, caused destructive behavior or metastasized, but numbers are too few and follow up too short to firmly establish a biologic potential. For now, cases falling into these two categories could be considered of "uncertain malignant potential".

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