Sinonasal Seromucinous Hamartoma: A Review of the Literature and a Case Report with Focal Myoepithelial Cells

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Abstract Seromucinous hamartoma is a benign lesion of the sinonasal tract. Since its description in 1974, only a small number of additional cases have been reported. It is composed of a proliferation of seromucinous glands and ducts within a variable fibrous stroma. The serous component typically stains positively for S100 (at least focally) and lacks p63 positive abluminal cells. The lack of myoepithelial/basal cells is an important diagnostic feature of seromucinous hamartoma; their absence could lead to an incorrect diagnosis of low-grade sinonasal adenocarcinoma. We report the case of a polypoid mass resected from the posterior nasal cavity and nasopharynx of a 54-year-old woman. The lesion contained a population of small and large glands lined by cuboidal to flattened cells within a hypocellular stroma varying from dense and sclerotic to myxoid. Additionally, there was a superficial focus of ciliated invaginated surface epithelium and glands. Throughout the lesion there were no cytologic or architectural features of malignancy. The histologic features

were diagnostic of seromucinous hamartoma. Immunohistochemistry showed focal S100 positivity of the serous glands. However, in contrast to previously reported cases, the glands focally showed an outer basal layer that was calponin, p63 and actin positive. Our case demonstrates two important points. First, complete absence of p63 staining should not necessarily be a required feature in the diagnosis of seromucinous hamartoma. Second, the ciliated larger glands—in keeping with respiratory epithelial adenomatoid hamartoma (REAH)—support the suggestion that seromucinous hamartoma and REAH are a spectrum of lesions, often seen together.

Keywords Seromucinous hamartoma · Respiratory epithelial adenomatoid hamartoma · Low-grade sinonasal adenocarcinoma · Nasal tumors

Introduction

Seromucinous hamartoma is a rare lesion of the sinonasal tract. The entity was initially described by Baillie and Batsakis in 1974 [1] as a single case report. Since then, 20 additional cases have been reported in the English literature [2–8] (Table 1). The male to female ratio is approximately 1:1. Patients are most often middle-aged to elderly (mean age 56) and present with symptoms of obstruction or epistaxis which is often long-standing. With rare exceptions, cases have arisen in either the posterior nasal cavity or the nasopharynx. The lesion is benign; after treatment with surgical excision there have been no documented metastases and only one report of a recurrence. Grossly, a seromucinous hamartoma is described as a polypoid mass which ranges in size from 0.6 to 6.0 cm. Histologically, the mass is covered by respiratory epithelium, and is

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Table 1 Cases of seromucinous hamartoma reported in the english literature

Author	Sex	Age	Location	Size	Follow-up (FU)
Baillie and Batsakis 1974 [1]	M	26	Posterior oropharynx	4.0 cm	2.5 years No recurrence.
Zarbo and McClatchey 1983 [2]	M	32	Midline superior nasopharynx	1.0 cm	2 years No recurrence.
Graeme-Cook and Pilch 1992 [3]	F = 3	57, 67, 78	Posterosuperior, posterior nasal cavity, nasopharynx	2.0, 5.0, 6.0 cm	4 months–1 year No recurrence.
Chuang and Lin 2000 [4]	M	54	Paranasal sinus	Not reported	6 months No recurrence.
Weinreb et al. 2009 [5]	M = 4 F = 3	14–85 (mean 56)	Posterior/septal = 6 Middle meatus/lateral nasal wall = 1	0.6–4.0 cm	6–60 months Five with no recurrence. 1 lost to FU 1 recurrence
Ambrosini-Spaltro et al. 2010 [6]	M = 2 F = 3	49, 50, 52, 63, 66	Nasal cavity = 4 Septum = 1	1.0–3.5 cm	1–8 years 1 lost to FU
Figures et al. 2010 [7]	M	75	Anterior midline nasal cavity with skull base involvement	Not reported	10 months No recurrence.
Khan et al. 2011 [8]	F = 2	61, 59	Right sphenothmoid recess, right nasal cavity	2.6 cm, not reported	10 months and 3.5 years No recurrence.

comprised of lobular or haphazard proliferations of small to large glands and ducts which are lined by a single layer of cuboidal or flattened epithelial cells. Nuclei appear monomorphic with no cytologic atypia. Eosinophilic cytoplasmic granules and clear-cell change are occasionally seen [5]. Eosinophilic secretions are often present within tubules. The surrounding fibrous stroma is usually variable and often contains a lymphoplasmacytic inflammatory infiltrate. Periglandular hyalinization has been reported in three cases [5]. Architectural features of malignancy such as back-to-back glands, cribriform patterns, and invasion are not seen. Two recently published case series [5, 6] have determined that seromucinous hamartomas are positive for CK7 and CK19, and negative for CK14 and CK20. The serous glands are usually S100 positive (at least focally), and are negative for p63 and muscle-specific antigen. Laminin and high-molecular-weight-keratin (HMWK) staining is variable.

Respiratory epithelial adenomatoid hamartoma (REAH) is another type of rare, benign lesion found in the sinonasal tract. It shares many clinical and histologic features with seromucinous hamartoma, though it is slightly more common and has a male predominance [9]. The lesion is a polypoid mass composed of a proliferation of glands lined by ciliated respiratory epithelium that invaginates from the surface. It often demonstrates periglandular stromal hyalinization, and there is often a mixed inflammatory infiltrate within the stroma.

Case Report

A 53-year-old female presented with a three year history of obstructed right nasal airway. A CT scan demonstrated a $3.7 \times 1.9 \times 2.6$ cm mass in the right posterior nasal cavity extending into the nasopharynx (Fig. 1). The mass was excised and there has been no recurrence at twenty-four months post-operatively. Grossly the lesion was a homogeneous, cream-colored, polypoid mass with a smooth surface. Microscopically, the lesion contained a mixed population of small and larger glands within a hypocellular stroma varying from dense and sclerotic to myxoid (Fig. 2). The glands were lined by cuboidal to flattened cells without appreciable cytologic atypia. In addition, there was a superficial focus of ciliated surface epithelium which invaginated downward to form large glands. This REAH-like focus merged with the serous component (Fig. 3). There were no architectural features of malignancy.

Immunohistochemical stains showed that both serous and respiratory glandular epithelial cells were positive for CK7, CK19, and HMWK. CK20 was negative. In contrast to previous reports in which p63 staining of serous glands has been negative, there were scattered p63 positive cells in most of the serous glands (Fig. 4). The REAH-like epithelium showed continuous p63 positivity of the basal layer. Within the serous glands there was also focal basal staining for calponin, actin, α -actin, and heavy chain myosin. S100 showed patchy, weak staining.

Fig. 1 Axial CT of maxilla. Note occlusion of right posterior choana and nasopharynx by mass (outlined by arrows)

Fig. 2 Seromucinous hamartoma, composed mostly of small glands within a fibrous stroma (40×)

Discussion

Although seromucinous hamartoma is a rare lesion, it is important that surgical pathologists be aware of its existence. The lack of p63 positive staining seen in most seromucinous hamartomas could be a diagnostic pitfall leading to an erroneous diagnosis of malignancy. The main differential diagnosis for seromucinous hamartoma is low-grade sinonasal adenocarcinoma, non-intestinal type (LGSNAC) [10]. Like seromucinous hamartoma, LGSNAC consists of glandular proliferations lined by cuboidal

Fig. 3 Seromucinous hamartoma with focal REAH-like invagination of respiratory epithelium and budding of serous glands (100×)

Fig. 4 Seromucinous hamartoma with p63 staining showing scattered positivity in proliferating serous glands (100×)

to columnar cells which are usually monomorphic and cytologically bland. Mitoses are rare and necrosis, perineural invasion and lymphovascular invasion are absent. Stromal invasion may or may not be appreciated. However, in contrast to seromucinous hamartoma, LGSNAC typically has complex growth patterns including micropapillary architecture, and glands which are back-to-back or fused. Immunohistochemistry is not helpful in separating seromucinous hamartoma and LGSNAC, as both are negative for CK20 and positive for CK7, CK19 and S100 [5, 6, 10]. In both entities p63 is usually negative. Although there have been no convincing reports of metastasis from LGSNAC, rare recurrences have been noted and local invasion and destruction of tissue can occur [11, 12]. Thus, it is important to distinguish seromucinous hamartoma from LGSNAC, as the latter may require more extensive surgery and possibly radiotherapy.

Two reported case series have examined the immunohistochemical profile of seromucinous hamartoma. Both Weinreb et al. (n = 5) and Ambrosini-Spaltro et al. (n = 5) reported negative p63 staining throughout the serous glandular component in all cases. Ours is the first reported case in which there is scattered p63 and actin positivity within the proliferative glandular epithelium. Therefore, we believe that a complete absence of myoepithelial/basal cells should not be a required feature of seromucinous hamartoma. Their presence may facilitate differentiation from LGSNAC in difficult cases.

The focal myoepithelial/basal cell layer identified within this lesion also raises within the differential diagnosis the salivary gland tumors that have a bilayered tubular appearance, including adenoid cystic carcinoma (tubular type), epithelial-myoepithelial carcinoma, and basal cell adenocarcinoma. As in our case, the luminal cells in each of the former salivary gland tumors are positive for CK7 and CK19 [13], and the nonluminal cells stain positively for p63 and other myoepithelial stains [14, 15]. However, these tumors can usually be excluded on H&E microscopy. The basal cell/myoepithelial component of adenoid cystic carcinoma, epithelial-myoepithelial carcinoma, and to a lesser extent basal cell adenocarcinoma is typically visible without immunostains. In addition, these tumors exhibit other growth patterns, cell types and/or evidence of invasiveness (e.g. perineural invasion) not found in seromucinous hamartoma [16].

Recently, Weinreb et al. suggested that seromucinous hamartoma and REAH may actually be a spectrum of lesions rather than two separate entities. Both lesions have similar presenting symptoms and are commonly found in the posterior nasal cavity or nasopharynx. They are both associated with inflammation. In addition, foci of seromucinous hamartoma are frequently found in REAH, and vice versa [5, 6, 8, 9]. Our case also demonstrates focal REAH-like features, and supports the suggestion that REAH and seromucinous hamartoma are related lesions. The etiology of both seromucinous hamartoma and REAH is unknown; whether they actually represent benign neoplasms rather than hamartomas is being debated.

Ambrosini-Spaltro et al. [6] extracted mitochondrial DNA (mtDNA) from normal tissue and from the proliferating tubules of five cases of seromucinous hamartoma. Using polymerase chain reaction (PCR) they analyzed the mitochondrial D-loop sequences, and determined that compared to normal tissue, the seromucinous hamartomas had a higher mean mtDNA mutation rate, especially in heteroplasmy (a mixture of wild type and mutant DNA). The mutation rate in homoplasmy (all mitochondria contain the same mutation) was only slightly increased. Previous literature has found that in a variety of cancers, cells have an increased rate of mtDNA homoplasmic mutations

[6], while in benign nasal polyps, there is an increase in heteroplasmic mutations [17]. The authors concluded that the absence of morphologic features of malignancy and the presence of mtDNA mutations in heteroplasmy are indicative of a benign lesion. However, they did not specifically conclude that the seromucinous hamartoma is neoplastic.

Another study by Ozolek and Hunt [18] compared the molecular profiles of ten cases of normal respiratory sinonasal mucosa, ten cases of REAH and nine cases of sinonasal adenocarcinoma (SNAC) (four intestinal type and five non-intestinal type). PCR was performed on DNA extracted from paraffin-embedded tissue using primers for four different tumor suppressor genes (CDKN2/p16, HRAS, p53 and DCC/DPC4). For each case the loss of heterozygosity ratio and the fractional allelic loss (FAL) were determined. Chronic sinusitis had a low FAL (2%), REAH had an intermediate FAL (31%), and SNAC had a high FAL (64%), leading the authors to suggest the possibility that REAH may be a benign neoplasm rather than a hamartoma.

Weinreb [19], in a recent review of low grade glandular lesions of the sinonasal tract, comments that the typical features of both REAH and seromucinous hamartoma can focally be seen within inflammatory lesions as well as within normal sinonasal mucosa. He also observed that these foci can have inconsistent myoepithelial staining. We also have noted focal REAH and seromucinous hamartoma-like features with inconsistent myoepithelial staining in chronic sinusitis and adjacent to sinonasal squamous cell carcinoma (unpublished data). These observations tend to support the suggestion that REAH and seromucinous hamartoma may represent reactive rather than neoplastic lesions. More investigation is required into this subject.

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