Seromucinous Hamartoma of the Nasal Cavity: A Report of Two Cases and Review of the Literature

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Received: 28 March 2011 / Accepted: 14 May 2011 / Published online: 27 May 2011
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Abstract The sinonasal tract is a complex anatomic site, home to a wide variety of reactive, inflammatory, benign, and malignant lesions. Inflammatory polyps and papillomas are usually easily recognized by pathologists. A poorly understood lesion that has been more clearly defined in recent years is the nasal hamartoma. The epithelial subtypes include seromucinous hamartoma, respiratory epithelial adenomatoid hamartoma, and hybrid lesions. Seromucinous hamartomas have only been recognized and substantially reported over the past few years. They are a diagnostic challenge, needing to be distinguished from low grade adenocarcinomas, and are of interest because most of the basic questions about their pathophysiology remain unanswered. Herein, we present two novel cases of seromucinous hamartoma with features that partly expand the morphologic spectrum of these lesions, discuss the differential diagnosis, and review the literature to compare our findings with previously reported cases with the aim of better understanding this interesting entity.

Keywords Seromucinous hamartoma · Microglandular adenosis · Low grade adenocarcinoma · Nasal cavity · Respiratory epithelial adenomatoid hamartoma

Introduction

Hamartomas are rare, tumor-forming, benign lesions that have been reported throughout the body. The term is somewhat controversial in that hamartomas are classically defined as a collection of cells or tissues normal for the given anatomic site but which are abnormal in amount, ratio, or distribution. They are, in theory, developmental in nature. However, most examples are not present at birth or in childhood, but rather develop in adulthood. This suggests that they represent benign neoplasms, a contention supported by some molecular studies [1, 2]. In the sinonasal region, hamartomas have been designated as epithelial, mesenchymal, and mixed [3, 4]. They include chondromesenchymal hamartoma [4–7], respiratory epithelial adenomatoid hamartoma (REAH) [8–11], and seromucinous hamartoma (SH). Each of these has characteristic features, but occasional lesions will show overlapping features of multiple types. They all pursue a benign course with only rare reports of recurrence. SH, although first described in 1974 by Baillie and Batsakis [12], is really the newest of these entities, having only been more clearly described and characterized in the past several years [13–15]. Herein, we report two additional cases of SH that partly expand their histologic spectrum and review the typical histologic features, differential diagnosis, and literature pertaining to these interesting lesions.

Case 1

Clinical History

A 61-year-old woman presented with an episode of delirium. During her workup, she underwent magnetic

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resonance imaging (MRI) and computed tomography (CT) scans of the head which incidentally revealed a nasopharyngeal mass. There was no other relevant clinical history. She was evaluated in the otolaryngology clinic and fiberoptic endoscopy showed a papillomatous lesion in the nasopharynx emanating from the right nasal cavity. She subsequently underwent endoscopic sinus surgery. Intraoperatively, a pedunculated, 2–3 cm, benign-appearing, papillomatous lesion based in the right sphenothmoid recess was found hanging into the nasopharynx. A simple excision was performed.

Pathologic Findings

The specimen consisted of a 2.6 cm, tan-pink, multinodular mass with an apparent stalk. Histologic sections revealed a papillary lesion with a central, solid core of edematous stroma, variably-sized vessels and mild chronic inflammation, including occasional plasma cells and rare eosinophils. The periphery had numerous broad-based projections (Fig. 1a, b) lined by ciliated, pseudostratified respiratory epithelium. Scattered, invaginated foci of surface respiratory epithelium were present, some of which contained inspissated mucus (Fig. 2a). Approximately 20% of the submucosa of the papillae contained irregular collections of bland, completely mature serous-type glands without obvious ducts (Fig. 2b, c). There was no epithelial proliferation, tufting, cribriforming, squamous metaplasia, or dysplasia, and the invaginations of respiratory epithelium lacked any significant degree of thickened or hyalinized basement membrane material.

Fig. 1 Seromucinous hamartoma (case 1) showing **a** a complex, arborizing, polypoid lesion with a loose, pale stroma (20× magnification) with **b** a lining composed of ciliated respiratory epithelium overlying the submucosa containing scattered, bland, seromucinous glands (40× magnification)

Fig. 2 Seromucinous hamartoma (case 1) showing **a** a loose submucosa with a mixture of bland seromucinous glands (*left*) and scattered invaginations of respiratory epithelium without pericellular basement membrane hyalinization (100× magnification). **b** Note the haphazard proliferation of seromucinous glands, which lack any

epithelial tufting, back to back growth or cribriforming (200× magnification). **c** The seromucinous glands have scattered, eosinophilic zymogen granules and round, regular nuclei without atypia or mitotic activity (400× magnification)

Clinical Follow Up

The patient recovered well from the surgery and was alive, symptom-free, and disease-free at last follow-up 10 months later.

Case 2

Clinical History

A 59-year-old woman was found to have mild paranasal sinus disease on an MRI study of the brain that was performed to evaluate her for a seizure disorder. Recommended follow-up CT scanning performed 3 months later

Fig. 3 Seromucinous hamartoma (Case 2) showing **a** a complex, polypoid lesion with more dense, eosinophilic submucosa (20× magnification) which has **b** abundant, haphazard seromucinous glands and scattered respiratory epithelial lined invaginations (40× magnification)

showed a right nasal polyp. At the time, she was asymptomatic, denying any pain, epistaxis, or airway obstruction. She underwent trans-nasal excision of the polyp at an outside facility where the pathologist rendered a diagnosis of low-grade adenocarcinoma arising in a REAH. The patient presented to our department for adjuvant radiation therapy. Before initiation of any treatment, the case slides were obtained from the outside facility and reviewed in house.

Pathologic Findings

Histologic sections showed a polypoid lesion lined by unremarkable pseudostratified, ciliated, columnar (respiratory) epithelium (Fig. 3a). The epithelium invaginated into the underlying stroma focally producing scattered dilated, cysts, some of which could be seen connecting to the surface, and occasional ones showing slightly thickened, eosinophilic basement membranes (Fig. 3b). Adjacent to the cysts were aggregates of small seromucous glands arranged in a vaguely lobular, but predominantly haphazard pattern, and partially surrounded by an eosinophilic, slightly fibrotic stroma with mixed chronic inflammatory cells (Fig. 4a). The glands lacked papillae, tufting, and cribriforming and, although prominent and haphazard, did not show infiltrative growth or confluent, back to back architecture. Foci of glandular atrophy were noted (Fig. 4b). The constituent cells were cytologically bland without cellular atypia or mitosis (Fig. 4b, c). The lesion was diagnosed as a benign hamartoma.

Clinical Follow Up

Due to the initial diagnosis of adenocarcinoma, the patient was taken back to the operating room for exploration and re-excision of the prior surgical site. No focal lesions were present endoscopically, and the excised tissue showed only mild chronic inflammation. No further treatment was undertaken, and the patient was alive, disease free, and symptom free at last follow up 3.5 years later.

Discussion

To date, 19 cases of SH have been reported in the English language literature [12–18], exclusive of the two described here (Table 1). They typically arise on the posterior nasal septum or in the nasopharynx, although they have also been described on the lateral nasal wall and in the paranasal sinuses [15]. The age at diagnosis varies between 14 and 85 years. The male to female ratio is 3:2.

The most common presenting symptoms are nasal obstruction and epistaxis, although most patients are

Fig. 4 Seromucinous hamartoma (Case 2) showing **a** a fibrotic submucosa with a mixture of bland seromucinous glands and slightly cellular, fibrous stroma with bland spindle cells (100× magnification). **b** Focally, the seromucinous glands had a more atrophic lining with cells containing less cytoplasm but still retaining bland, round,

hyperchromatic nuclei (200× magnification). **c** The seromucinous glands retained eosinophilic cytoplasmic zymogen granules and lacked any back to back growth, epithelial tufting, papillae or destructive growth (200× magnification)

Table 1 Summary of reported cases of seromucinous hamartoma, exclusive of the current cases

Authors	Cases	Age	Sex	Location	Outcome
Baillie et al.	1	26	M	Nasopharynx	Patient was alive and disease free after 2.5 years of follow up.
Zarbo et al.	1	32	M	Nasopharynx	Patient was alive and disease free after 2 years of follow up.
Graeme-Cook et al.	3	57–78; Mean 68	F	Posterior nasal cavity ×2, nasopharynx ×1	All the patients were alive and disease free after 4 months to 1 year of follow up.
Chuang et al.	1	54	M	Paranasal sinus	Patient was alive and well after 1.3 years of follow up.
Weinreb et al.	7	14–86; Mean 56	4 M 3F	Nasal cavity; posterior septum ×6 and lateral wall ×1	4 patients were alive and disease free after 0.5–5 years of follow up. One patient had a local recurrence and was alive and disease free after second resection.
Ambrosini-Spaltro et al.	5	49–66; Mean 56	3F 2 M	Nasal Cavity (one from nasal septum; others not further specified)	4 out of 5 patients had follow up. All were alive and disease free after 1–8 years of follow up.
Figures et al.	1	72	M	Nasal cavity; superior septum with bilateral involvement	Patient was alive and disease free after 10 months of follow up.

asymptomatic and the lesions found incidentally. Some patients with SH also have coexistent medical conditions, such as rheumatoid arthritis, Parkinson disease, and chronic sinusitis, although a clear causal or etiologic relationship with other diseases has not been established. Physical examination normally reveals a polypoid mass without any local invasion, bone destruction, or other aggressive features.

Microscopically, SH was initially described as consisting of a polypoid mass of respiratory–epithelium-lined tissue with submucosal seromucinous glands in a lobular arrangement and a fibrous background [12]. Subsequent case reports highlighted additional features, such as invaginated, ciliated respiratory epithelium-lined gland-like structures in

a haphazard arrangement [18] with squamous metaplasia and a dense lymphoplasmacytic infiltrate [17]. Additional cases revealed the presence of dense cytoplasmic eosinophilic granules, consistent with modified zymogen granules, plus clear cell changes and periglandular hyalinization. Immunohistochemistry showed diffuse positivity for cytokeratins 17 and 19 and demonstrated the absence of myoepithelial cells among the seromucinous glands [15]. Moreover, these cases suggested that basement membranes were intact around the gland-like structures, as evidenced by positive collagen IV and laminin immunostaining [15], a finding further supported by Ambrosini-Spaltro et al. [13] in their five cases.

The differential diagnosis for SH includes inflammatory polyp, REAH, and low grade non-intestinal type adenocarcinoma. SH has a prominent glandular component, which inflammatory polyps lack, and although it has stromal edema, this is more prominent in inflammatory polyps, which arise in the setting of chronic inflammation leading to the accumulation of fluid in the submucosa. This characteristic degree of edema obliterates minor salivary gland tissue from inflammatory polyps, whereas SHs are rich in these glands. In addition, the surface of inflammatory polyps is smooth because the lesions form by outward expansion, whereas virtually all SH will have at least a partially convoluted, polypoid surface (Fig. 1).

REAH, though rare, is the most common hamartoma of the sinonasal tract. It was first described by Wenig and Heffner as a benign overgrowth of submucosal ciliated respiratory lined glands forming a polypoid mass lesion [11]. The majority arise from the posterior nasal septum, more commonly in males between the ages of 27 and 81, who present with obstructive symptoms or epistaxis [9–11]. It was suggested that they may be associated with other lesions, such as inverted papilloma and solitary fibrous tumor, but no definite precursor lesions have been identified [3].

REAH is composed of closely packed invaginations of respiratory epithelium, some showing connection to the surface, with periglandular hyalinization and minimal intervening stroma. The epithelium is bland and mature, although uncommonly one can see attenuated epithelium that appears collapsed (atrophic). Focal hyperplasia of the adjacent seromucinous glands [19], a typical finding of SH, may also be present. This is a common overlapping feature between REAH and SH, in addition to their common origins in the posterior nasal cavity and septum. Many cases of SH show localized REAH like changes with glands and cysts lined by invaginated respiratory epithelium, although this is usually only focal [15]. Similarly, many cases of REAH show seromucinous glands [19]. As such, they may simply represent a continuum of changes that have been somewhat arbitrarily divided. The term chondro-osseous REAH has been used to describe examples of REAH distinguished by the presence of either cartilage or bone [19, 20]. These may represent a hybrid lesion comprised of both REAH and chondromesenchymal hamartoma together. Inflammatory nasal polyposis often precedes or coexists with REAH. However, these inflammatory polyps are thought to be reactive rather than associated lesions [19]. Immunohistochemistry is not usually necessary to make the diagnosis but the respiratory epithelium of REAH is positive for cytokeratin 7 and negative for cytokeratin 20, CDX2, S100 and p63, while the basal layer of the gland-like structures is positive for 34betaE12 [20]. To date, there have been no examples of REAH with

aggressive behavior or convincing examples of recurrence after complete excision [11, 19, 21].

The final and most important differential diagnostic entity is low grade non-intestinal type adenocarcinoma, as previously alluded to. The World Health Organization (WHO) classifies sinonasal adenocarcinomas into salivary and non-salivary types [22]. The salivary group consists of entities identical to their salivary gland counterparts so are easily differentiated from SH. The non-salivary group consists of intestinal (enteric) and non-intestinal type adenocarcinomas, each having low and high grade subtypes [19]. Intestinal type adenocarcinomas are aggressive tumors that are easily recognizable because of their striking similarity to intestinal epithelium and actual intestinal adenocarcinoma [23, 24]. Non-intestinal type adenocarcinomas are relatively heterogeneous and poorly defined and thus are generally considered as a diagnosis of exclusion [8, 19, 22]. While some cases are frankly malignant, it is the low grade non-intestinal type that is most likely to be confused with SH. This low-grade lesion is characterized by papillary projections, epithelial tufting, cribriform glands, trabeculae, and apical snouting of the cells. However, cellular atypia, nucleoli, and mitotic figures are frequently absent or limited. Destructive, infiltrative growth is an important feature but is frequently difficult to assess in exophytic lesions [8]. Immunohistochemistry in low grade non-intestinal adenocarcinoma shows positive staining for cytokeratin 7 and S-100. The lack of basal cells is supported by the absence in staining with p63 and cytokeratin 34betaE12, which nicely highlight the basal cells of the overlying normal respiratory epithelium [8]. As such, the immunoprofile overlaps completely with SH but is quite distinct from intestinal-type adenocarcinoma (i.e., CK20 and CDX2 positive). The histologic features of SH differ from adenocarcinoma by lacking all of these concerning features. In addition, SH should not have such dense or “back to back” glandular proliferation. Also, the presence of zymogen-type cytoplasmic granules in the glandular component strongly favors a benign lesion [13, 15]. However, as acknowledged by other authors [8, 19], the lowest end of low grade adenocarcinoma can be difficult, if not impossible, to discern from SH. In our opinion, some definitive features of malignancy must be demonstrated in order to make a diagnosis of adenocarcinoma. Given the overlap in features between SH, REAH, and low grade non-intestinal type adenocarcinoma in some cases, more studies are warranted to clearly define their relationships.

SH is virtually always cured by simple surgical excision. In the literature, only a single case with features of SH recurred, and interestingly, this lesion had hybrid features of both SH and REAH [13–18]. That patient underwent a simple re-excision and was well at last follow-up.

Our two cases are slightly different than what is typically described for SH. In case 1, the lesion consisted of a complex, polypoid mass in which the stroma was markedly edematous and “loose” with little chronic inflammation (Figs. 1, 2) and associated with only a minor component of proliferating seromucinous glands and rare invaginations of respiratory epithelium with minimal pericellular hyalinization. However, it did have the haphazard seromucinous gland proliferation characteristic of SH. This lesion was not an inflammatory polyp because it had a convoluted and arborizing architecture with numerous smaller, polypoid projections and a more significant amount of seromucinous glands. Inflammatory polyps develop by bulbous expansion of the stroma, excluding seromucinous glands secondary to increasing edema that results in a smooth external surface. Case 1 was not a REAH, either, because it had very minimal invagination of the respiratory epithelium without significant pericellular hyalinization.

In case 2, the proliferation of seromucinous glands was actually quite florid, haphazardly arranged and associated with a significant fibrous stroma (Figs. 3, 4). This component was much more prominent than usually reported for most SH [13, 15], and, as such, it mimicked a low grade adenocarcinoma. However, there was no evidence of epithelial proliferation within the glands, such as papillary or cribriform growth. There was also no atypia or mitotic activity nor evidence of confluent or frankly destructive growth of glands. The patient has had no evidence of recurrence 3 years after a simple excision without further treatment.

In summary, SH is a rare and unique form of nasal cavity hamartoma characterized by an arborizing, polypoid growth pattern lined by respiratory epithelium, and submucosa having a haphazard proliferation of seromucinous glands without atypia or frankly destructive, infiltrative growth. Although biologically and histologically distinct, they can be easily confused with simple inflammatory polyps. They are benign and virtually always cured by simple excision. In particular, the pathologist must be aware of the differential diagnosis so that the haphazard arrangement of the glands and, in particular, the occasional prominent fibrotic stroma mimicking infiltration, as seen in our second case, does not lead to the overdiagnosis of adenocarcinoma.

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