Low-Grade Epithelial Proliferations of the Sinonasal Tract

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Abstract Low-grade epithelial proliferations of the sinonasal tract include Schneiderian papillomas, respiratory epithelial adenomatoid hamartoma, seromucinous hamartoma and low-grade non-intestinal adenocarcinoma. There is considerable overlap in their clinical presentation, endoscopic appearance, and imaging features. Although well-described diagnostic criteria exist, a definitive diagnosis may be difficult to reach on a small biopsy. Schneiderian papillomas are divided into fungiform, inverted, and oncocytic types, each with characteristic clinical and morphological features. The latter two may progress to malignancy. The majority are still considered to be HPV-related. Two lesions are designated as hamartomas, but their pathogenesis remains uncertain, with inflammatory and neoplastic origins proposed. Respiratory epithelial adenomatoid hamartoma is increasingly being recognized for its association with chronic rhinosinusitis and olfactory cleft site of origin. Seromucinous hamartoma has gained attention in recent years and overlaps with both respiratory epithelial adenomatoid hamartoma and low-grade non-intestinal adenocarcinoma. Controversy surrounds their distinction, particularly from low-grade adenocarcinoma. The latter generally is cured by complete excision, with a 26 % risk of recurrence but rare metastases and deaths from disease.

Keywords Schneiderian papilloma · Respiratory epithelial adenomatoid hamartoma · Seromucinous hamartoma · Adenocarcinoma · Nasal cavity · Sinonasal tract

Introduction

Despite the myriad reactive and neoplastic lesions of the sinonasal tract, the number of purely epithelial low-grade entities is rather few. They include Schneiderian papillomas, encountered from time-to-time by most general surgical pathologists, and the distinctly uncommon sinonasal hamartomas and low-grade non-intestinal type adenocarcinoma (LGNIA). The source of these lesions is respiratory-type surface epithelium and seromucinous glands. The olfactory epithelium, which gives rise to olfactory neuroblastoma, does not have a benign low-grade counterpart.

Hamartomas and LGNIA in particular, may give rise to confusion and misdiagnoses, particularly on small biopsies and/or when clinical information is limited. This review will focus on these low-grade epithelial proliferations, emphasizing practical clinical and pathological clues to their diagnosis and differential diagnosis.

Schneiderian Papillomas

Background

Schneiderian papillomas are relatively uncommon, benign neoplasms that are named for the epithelium from which they arise: the ectodermally-derived, pseudostratified ciliated (PC) epithelium that lines much of the nasal cavities and the entirety of the nasal sinuses. Papillomas are divided

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into three categories: exophytic/fungiform (FSP), endophytic/inverted (ISP) and oncocytic/cylindrical cell (OSP) types. The published frequency of these subtypes varies by study, but the inverted type is the most common, accounting for nearly two thirds of cases. Fungiform and oncocytic types account for nearly one third and about 5 %, respectively [1–3]. The clinical and morphological features of each are quite distinct, and although some overlap exists, they should not be lumped together for diagnostic purposes as “Schneiderian papilloma” without further qualification.

The etiology of FSP and ISP has long been thought to be human papillomavirus infection, particularly with low risk HPV serotypes 6 and 11 [2, 4–6]. HPV DNA has been identified, using various techniques and combining the results of several studies, in approximately one third of papillomas [5]. The etiology of OSP is unknown. Papillomas are commonly associated with chronic rhinosinusitis, particularly ISP and OSP, but a causal association has not been proven. They typically occur in adults, with a mean age in the 6th decade for ISP and OSP, and slightly younger for FSP [1]. ISP and FSP are more common in men (male to female ratio of 3–4:1), with an equal gender distribution for OSP.

Exophytic/Fungiform Papilloma (FSP)

Clinical Features

FSP almost exclusively arise on the nasal septum (preferentially anterior), with a small minority involving or arising from the lateral nasal wall, turbinates, or vestibule [1]. Involvement of paranasal sinuses is extremely rare. They may be multiple, but are rarely bilateral. Presentation is with obstructive symptoms, epistaxis, or as an incidentally identified mass [1, 2]. Imaging studies are not typically performed, but might show soft tissue thickening along the septum, with no septal destruction.

Pathology

FSP are broad-based lesions, usually less than 2 cm in greatest dimension. They are often received nearly intact, with a base of normal tissue. Microscopically, they are composed of broad, branching papillae lined by multiple layers of transitional or mature squamous epithelium (Fig. 1a). Pure PC epithelium is less common, although ciliated cells may be found at the surface of the immature squamous epithelium. Occasional mitotic figures may be noted, particularly in transitional epithelium (Fig. 1b). Keratinization is absent or limited to a few layers of parakeratin, unless the papilloma has become irritated. Active inflammation may be associated with mild reactive atypia, but dysplasia is not seen.

Treatment and Prognosis

Treatment is with complete local excision. The rate of recurrence is up to 20 %, likely related to incomplete excision. There is essentially no risk of progression to squamous cell carcinoma, with this event limited to a rare case report [7].

Endophytic/Inverted Papilloma (ISP)

Clinical Features

ISP typically arises from the lateral nasal wall and/or sinuses, sometimes with involvement of multiple sinuses. Maxillary and ethmoid sinus involvement is most common. Septal origin occurs in a minority of cases. Symptoms include nasal obstruction, epistaxis, headaches, proptosis or symptoms of chronic rhinosinusitis. There are no pathognomonic radiographic features, but a suspicious CT scan may show a contiguous nasal cavity and sinus mass with unilateral sinus opacification (Fig. 2a). There may be focal hyperostosis or osteitis within the sinuses [1]. Pressure erosion of bone may occur, but not destructive invasion.

Pathology

Biopsy may precede definitive excision, in which case only small polypoid fragments of tissue are received. Definitive excision specimens of ISP often consist of one or more large polypoid fragments (sometimes several centimeters in greatest dimension), with multiple smaller pieces that include residual ISP and normal tissue (fragments of nasal mucosa, turbinate and sometimes bone). When received intact, the surface of a typical ISP is pale tan and cerebriform, with the “sulci” representing foci of invagination of epithelium into the stroma. The cut surface is variegated, with opaque ribbons of invaginating epithelium, surrounded by pale, edematous stroma (Fig. 2c, d).

Microscopically, the inverted component can include PC, transitional, and mature squamous epithelium in varying proportions. It forms elongated and lobulated islands of cells, sometimes branching or cystic, amid a loose, fibromyxoid stroma (Fig. 3a–c). Multiple sites of connection with surface epithelium are seen. Acute inflammation is common and sometimes extensive. Residual seromucinous glands are not usually identified or are few. The surface epithelium may be squamous or ciliated; the former may be keratinized and the latter may be hyperplastic (Fig. 4b). In some cases the inverted squamous cells may be clear (Fig. 3d); keratin pearls are not identified.

When squamous cell carcinoma arises in ISP, there is often an abrupt transition from benign to malignant (usually conventional or non-keratinizing squamous cell carcinoma). The malignant epithelium may have a similar nested pattern

Fig. 1 Fungiform Schneiderian papilloma. **a** Papillary architecture with a central core arising from the nasal mucosa. **b** Transitional epithelium without surface keratinization. Note mitotic figure in a suprabasal location

Fig. 2 Inverted papilloma. **a** Coronal CT scan showing involvement of left nasal cavity, maxillary and ethmoid sinuses with hyperostosis of lateral wall of maxillary antrum. **b** Endoscopic view; note polypoid architecture. **c** External surface showing cerebriform appearance.

d Cut surface showing inverted pale tan ribbons of cells, extending into myxoid vascularized stroma. (CT and endoscopic images courtesy of Dr. E. Massoud, Department of Surgery, Dalhousie University)

to the ISP, raising the possibility of in situ disease. However, when this pattern is extensive it is commonly associated with desmoplastic stroma, and is consistent with invasion

(Fig. 5a, b). In the author's experience, low-grade dysplasia as an identifiable precursor lesion is not common in ISP with malignant transformation.

Fig. 3 Inverted papilloma. **a** Closely-packed islands of inverted cells with lobulated architecture. **b** Squamous epithelium with inflammation. **c** Islands of cells lined by preserved respiratory epithelium, forming small cysts. **d** ISP containing largely clear cells

Fig. 4 Variations in inverted papilloma. **a** Islands of cells with relatively thin respiratory epithelium, resembling REAH. Note lack of distinct periglandular hyalinization. **b** Hyperplasia of epithelium on the surface of an ISP

Treatment and Prognosis

Definitive treatment for ISP is medial maxillectomy: resection of the lateral wall of the nasal cavity and removal

of the ipsilateral sinus mucosa and mucoperiosteum. The rate of recurrence with this approach is less than 20 %, much lower than by removal by snare and avulsion [8]. Recurrence is more likely in frontal sinus papillomas, due to

Fig. 5 Squamous cell carcinoma arising in an ISP. **a** Abrupt transition from non-dysplastic ISP (*upper and right*) to squamous cell carcinoma (*lower and left*). **b** Invasive carcinoma with stromal desmoplasia and keratinization

the technical difficulty of operating at this site [9]. Unlike ESP, there is a significant risk of progression to malignancy, usually squamous cell carcinoma, but occasionally verrucous or adenocarcinoma. Carcinomas may be synchronous or metachronous, more commonly the latter. In a large series of 1390 ISP, 11 % were associated with carcinoma [10].

Oncocytic/Cylindrical Cell Papilloma (OSP)

Clinical Features

These tumors have a predilection for the nasal sinuses (maxillary, ethmoid) and lateral nasal wall [2, 11]. They present similarly to ISP and when recognized correctly as a papilloma by the otolaryngologist, are rarely suspected to be OSP.

Pathology

The gross appearance of OSP is a fleshy, pink-tan, polypoid mass. It has a combined inverted and exophytic growth pattern, the latter consisting of non-branching papillae that are sometimes quite elongated (Fig. 6a, b). From low power, there is a characteristic eosinophilic “fringe” of proliferating cells along the surface, which combined with numerous intraepithelial microabscesses, is nearly pathognomonic (Fig. 6c, d). The cells are organized in a pseudostratified fashion and are ovoid to columnar in shape, with eosinophilic, granular cytoplasm. The nuclei are uniform and may contain easily visible nucleoli. Residual mucocytes, intraepithelial microabscesses and microcysts are common. Dysplasia is not typically identified.

Treatment and Prognosis

The treatment is with complete surgical excision, sometimes requiring medial maxillectomy, as for ISP. Approximately one third recur. Malignant transformation may also occur, but it is uncommon and limited to case reports or small series [12, 13].

Differential Diagnosis of Schneiderian Papillomas (Table 1)

FSP and ISP are usually easily distinguished from each other by history and low power architecture. However, if FSP is cut tangentially and/or if only small portions are received, the epithelium may appear sufficiently hyperplastic and lobulated as to appear invaginated. Resection specimens of FSP will typically show a point of attachment and “mushroom-like” projection above the surrounding mucosa, with residual seromucinous glands at the base. In contrast, ISP forms a polypoid mass, with a smooth or gently undulating surface. Stroma is prominent in ISP and residual seromucinous glands are not identified, except in uninvolved, separate mucosal fragments. Rare, short, broad papillae may be identified in ISP, but they lack the complexity of FSP. As a general rule, lesions with any genuine inverted morphology should be considered ISP, and the author would discourage the term “combined” morphology, for fear of improper follow-up.

FSP is more often confused with verruciform lesions from the anterior nasal vestibule, which is lined by skin. This includes verruca vulgaris and generic “squamous papillomas” of skin origin. Careful attention to site of origin and the presence of skin adnexae will usually permit

Fig. 6 Oncocytic Schneiderian papilloma. **a** Exophytic component showing long papillae with eosinophilic cells forming a “fringe”. **b** Combined exophytic and endophytic components. **c, d** Proliferating oncocytic epithelium with mucous microcysts and microabscesses

distinction. The skin lesions are often heavily keratinized, and verruca vulgaris in particular has a characteristic “wedge-shaped” architecture.

The architecture of FSP may raise the possibility of papillary/exophytic squamous cell carcinoma (PSCC). However, the epithelium of PSCC is frankly malignant, with disorganization, crowding and frequent mitotic figures that extend close to the epithelial surface. Recently, Lewis et al. described a deceptively bland papillary carcinoma in a 47-year-old woman that was initially thought to be a Schneiderian papilloma, but which recurred numerous times over an 18 year period (requiring orbital exenteration), with the development of lymph node metastases. The patient eventually died from her disease. The case report images show a combined exophytic and endophytic mass, somewhat resembling a low-grade papillary urothelial carcinoma. They have labelled this entity “Low-grade Papillary Schneiderian Carcinoma” [14]. So far, this appears to be a unique case.

ISP can be confused with non-keratinizing/transitional squamous cell carcinoma (NKSCC), which frequently has

a nested or lobulated pattern of invasion and can be rather monomorphous. Again, the distinction is based on the greater degree of atypia, mitotic activity, and necrosis in NKSCC. Well-differentiated conventional squamous cell carcinoma may invade in large rounded islands, but it is associated with keratinizing dysplasia of the surface, and squamous atypia and keratin pearls in the invasive component. Verrucous carcinoma is exceedingly rare in the sinonasal tract. It has heavy, “church spire”-like parakeratosis and broad-based, endophytic growth that would rarely be confused with FSP or ISP, except in a superficial biopsy.

Finally, the differential diagnosis for ISP includes respiratory epithelial adenomatoid hamartoma (REAH). This distinction will be made in the discussion of REAH that follows.

OSP is morphologically very characteristic. For the uninitiated, the source of confusion is often with some form of low-grade adenocarcinoma. The elongated papillae would be unusual for nasal adenocarcinomas, and the inverted component of OSP forms large islands with

Table 1 Differential diagnosis of Schneiderian papillomas

Type	Differential diagnosis	Key differentiating features (found in differential entity)
FSP ^a	Nasal skin papilloma	Presence of skin adnexae Keratinization Lack of residual ciliated cells or mucocytes
FSP	Papillary SCC ^b	Malignant epithelium (resembling carcinoma in situ)
ISP ^c	Non-keratinizing SCC	Atypia, mitotic activity, necrosis
ISP	Conventional SCC (not ex ISP)	Keratinizing dysplasia Atypia, desmoplasia, deep keratinization Lack of cilia
ISP	REAH ^d	Septum or olfactory cleft Respiratory epithelium of normal thickness, no transitional metaplasia Prominent periglandular hyalinization Some small glands
OSP ^e	Adenocarcinoma (not otherwise specified)	Lack of elongated papillae Atypia, mitoses Complex glandular architecture with fusion, stromal desmoplasia Oncocytic morphology rare
OSP	Rhinosporidiosis	Sporangia located in stroma Pseudoepitheliomatous hyperplasia Lack of oncocytes

^a Fungiform Schneiderian papilloma^b Squamous cell carcinoma^c Inverted Schneiderian papilloma^d Respiratory epithelial adenomatoid hamartoma^e Oncocytic Schneiderian papilloma

elongated lumens and intact basement membrane, rather than back-to-back glands. Residual mucocytes are dispersed and distributed at different levels within the epithelium, rather than lining a lumen. There is no significant atypia or mitotic activity in OSP.

OSP may be confused with rhinosporidiosis, which also can present as a polypoid lateral nasal mass. The intraepithelial mucocysts of OSP may resemble the sporangia of rhinosporidiosis, but the latter are found in the stroma rather than the epithelium, sometimes associated with pseudoepitheliomatous hyperplasia. Oncocytic metaplasia and exophytic papillary architecture is not identified in rhinosporidiosis.

Hamartomas of the Sinonasal Tract

Background

Two epithelial entities categorized as hamartomas are included here, respiratory epithelial adenomatoid hamartoma (REAH) and seromucinous hamartoma (SMH).

Lesions showing hybrid REAH and SMH features are also described, and they may represent a disease spectrum. REAH was first described by Wenig and Heffner in 1995 as a series of 31 cases [15]. Since then, multiple case reports and series have been published [16, 17]. SMH was first described in 1974 as a single case report of a nasopharyngeal “glandular (seromucinous) hamartoma” [18]. There were scattered case reports in the intervening years, but SMH has been resurrected in earnest over the last 6 years, primarily because of its relationship to REAH and unique immunoprofile [19–22].

The exact nature of REAH and SMH is debated and reactive, hamartomatous and neoplastic origins have been proposed. REAH is commonly associated with chronic sinusitis and nasal polyps, suggesting an inflammatory origin [16, 17, 23]. However, Ozolek and Hunt proposed that REAH may be a benign neoplasm, based on a considerably higher percentage of fractional allelic loss (a relative measure of loss of heterozygosity) compared with isolated chronic sinusitis [24]. Further molecular studies to bolster this hypothesis are lacking.

An uncommon combined epithelial and mesenchymal hamartoma exists, with the glandular component of REAH and central ossification. This is called “chondro-osseous and respiratory adenomatoid hamartoma” (CORE hamartoma) [25]. It is best considered a subtype of REAH.

Respiratory Epithelial Adenomatoid Hamartoma (REAH)

Clinical Features

REAH presents with symptoms of nasal obstruction/congestion, rhinorrhea, hyposmia, headache, facial pain, or epistaxis. It is more commonly associated with chronic rhinosinusitis and polyposis, rather than presenting as an isolated lesion. It occurs in adults from the 3rd to 9th decade (peaking in the 6th) and is up to 7 times more frequent in men. Although classically described in a posterior septal

location, many appear to arise within the olfactory cleft (a narrow chamber located beneath the cribriform plate). They may also involve in the lateral nasal wall, nasopharynx, and paranasal sinuses [15–17, 23]. Bilaterally is common, up to 37 % in one study [16]. Radiologically, the mass may cause sinus opacification and/or widening of the olfactory cleft, depending on location [16, 17]. The endoscopic appearance is of a polypoid, indurated mass, darker than an inflammatory polyp [16].

Pathology

Grossly, REAH is received as a polypoid mass or mucosal fragments, usually no more than several centimeters in greatest dimension. REAH is characterized by the presence of oval to elongated glands lined by PC epithelium, often extending into the stroma from the surface. The lesion may appear “stuck on” to the underlying tissue (Fig. 7a) or create a more polypoid mass. The glands are typically

Fig. 7 Respiratory epithelial adenomatoid hamartoma. **a** Low power image of a septal REAH with broad attachment to stroma. **b** Ciliated glands with pronounced periglandular hyalinization and intervening chronic inflammation. **c** Marked goblet cell metaplasia. **d** A more

polypoid REAH (exact site of origin unknown). Smaller seromucinous hamartoma-like glands arise near the tips of the ciliated glands, a feature not compatible with inverted papilloma

surrounded by thick, hyalinized stroma, which can occupy nearly the entire stromal component (Fig. 7b). Goblet cell metaplasia and/or chronic inflammation may be present (Fig. 7b, c). Other lesions have a greater amount of inflamed, loose stroma and less organized glands that may be cystically dilated (Fig. 7d). There is no significant atypia or mitotic activity. Associated proliferation of small seromucinous glands is common. Immunohistochemistry may not be required for diagnosis, but the ciliated epithelium is CK7 positive and CK20, CDX-2, S100 negative, with a complete peripheral rim of p63 positive basal cells.

Seromucinous Hamartoma

Clinical Presentation

Seromucinous hamartoma (SMH) may cause nasal obstruction or epistaxis, or is found incidentally during investigation for other conditions. There is a wide age range, from young adults to the elderly, which peaks in the late 6th decade, with a nearly even sex distribution. SMH is most commonly solitary and found on the posterior nasal septum or nasopharynx, but it may arise on the lateral nasal wall and rarely in the paranasal sinuses. They are polypoid masses that range from less than 1 cm to 6 cm in greatest dimension [19–22, 26, 27].

Pathology

Seromucinous hamartoma forms a polypoid mass, covered by respiratory epithelium. It is composed primarily of small glands with a single layer of cells, which may bud from larger ciliated glands. The glands are haphazardly arranged or lobular in configuration (Fig. 8a, b). The stroma is

edematous to fibrotic, with patchy chronic inflammation. The glands may be closely-packed, but are not fused or cribriform. The cells typically have pale eosinophilic, slightly granular cytoplasm. They may contain zymogen granules, but contrast with the more uniform coarse granularity and dark red to purple zymogen granules of normal serous acini. There is no atypia, mitotic activity, or epithelial proliferation (Fig. 9a, b). Immunohistochemistry shows CK7, CK19 and S100 positivity with a total (or near total) absence of basal cells, confirmed by the absence of periglandular p63 staining [19] (Fig. 9c, d). The latter feature contrasts with the p63-positive, periglandular basal cells of the ciliated glands.

Treatment and Prognosis

The treatment for both REAH and SMH is by endoscopic resection. Recurrence is infrequent and malignant transformation has not been reported. However, REAH may behave in a locally aggressive fashion if left untreated [16].

Differential Diagnosis

The main differential diagnosis for REAH is with ISP, with a primary clinical distinction being location (posterior septum vs lateral nasal wall, respectively). ISP may contain some elongated, ciliated glands (Fig. 4a), but these usually have thicker epithelium due to the presence of immature squamous metaplasia beneath the ciliated lining. Periglandular hyalinization is not prominent in ISP and conventional ISP features are usually identified elsewhere. REAH often contains a component of small seromucinous glands, whereas residual small glands are rare in ISP, as the proliferating epithelium completely replaces and expands the normal ductulo-acinar units.

Fig. 8 Two seromucinous hamartomas. Both show proliferations of small glands, which bud from elongated, ciliated glands. Note lobular configuration in (a)

Fig. 9 Seromucinous hamartoma. **a** Proliferation of small, bland glands with minimal intervening stroma. Note budding from ciliated gland in upper right. **b** Focus of SMH in a nasal polyp. Note the normal seromucinous glands on upper right, with more eosinophilic,

granular cytoplasm. P63 was retained around these glands. **c** p63 showing absence of staining around small glands. **d** S100 showing positivity of small glands

REAH may sometimes be confused with an adenocarcinoma, but the appearance does not fit with common low-grade nasal adenocarcinomas. The glands of REAH are larger and separate, with bland, PC epithelium. Intestinal type adenocarcinomas (ITAC) may have pseudostratification and goblet cells, but one would typically also find villous architecture, Paneth cells, dysplasia, or frankly malignant features. In ITAC there is an absence of cilia, p63 positive basal cells, and periglandular hyalinization. ITAC is CK20 and CDX-2 positive, whereas REAH is negative for both.

SMH may be confused with LGNIA and possibly with other low-grade adenocarcinomas. SMH is bland, without cytological or architectural features of malignancy (such as glandular fusion and invasion). The combined S100 positive, p63 negative phenotype is characteristic of SMH, as is the presence of “budding” from larger glands. Distinction from LGNIA is further discussed in the following section.

Foci with identical features to REAH and/or SMH may be seen incidentally in cases of chronic rhinosinusitis and

nasal polyposis. Gauchotte et al. reviewed 150 consecutive cases of nasal polyposis and discovered REAH lesions in 35 %, in a distribution that suggested an origin from the olfactory cleft. They concluded that REAH within a polyposis background is 20 times more common than solitary cases [23]. REAH-like glands are also sometimes found overlying nasal tumors, such as ISP and solitary fibrous tumor [15, 28]. Presumably, this is a hyperplastic phenomenon, and the term hamartoma should be reserved for polypoid, mass-forming lesions.

Sinonasal Low Grade Non-intestinal Type Adenocarcinoma (LGNIA)

Background

Primary sinonasal adenocarcinoma is discussed more thoroughly elsewhere in this issue. In brief, sinonasal adenocarcinomas may be of salivary or non-salivary type,

with the latter including intestinal type adenocarcinomas and non-intestinal adenocarcinomas, low- and high-grade [29]. Another rare low-grade entity, “sinonasal renal cell-like carcinoma” has recently been described, which has some overlapping features with LGNIA [30].

The concept of LGNIA has existed for more than 30 years [31] and the synonyms sinonasal tubulopapillary low-grade adenocarcinoma and terminal tubulus adenocarcinoma have been used. Similar tumors occur in the nasopharynx [32]. Some reported LGNIA have been associated with REAH, leading to controversy regarding the dividing line between reactive/hamartomatous small glandular lesions and low-grade adenocarcinoma [33].

Clinical Features

LGNIA may affect both children and adults (range 9–80 years), with a peak in the sixth decade. There is no sex predilection. There are no established risk factors. The most common presentation is non-specific, usually with

obstruction or epistaxis. They may occur anywhere in the sinonasal tract, but have a predilection for the ethmoid sinuses and lateral nasal wall, particularly the middle turbinate.

Pathology

LGNIA are typically exophytic or papillary growths, under 4 cm in greatest dimension. The architecture of these tumors is highly variable, sometimes within a single tumor (Fig. 10a–d). They form glandular, papillary, and microcystic patterns. The glands are closely packed with minimal stroma. The glands typically have only a single layer of cells, but some pseudostratification may be noted. There is no basal layer. The cells are cuboidal to columnar, with pale cytoplasm and little pleomorphism or mitotic activity. Perineural invasion and necrosis are not identified. Clear cell, oncocytes, and focal squamous differentiation have been described, and psammoma bodies are sometimes present. Malignancy is established by the complex, back-

Fig. 10 Low-grade non-intestinal adenocarcinoma. **a** Closely-packed glandular proliferation with minimal intervening stroma. **b** Small fused glandular pattern. **c** Microcystic pattern. **d** Solid/nested pattern

with occasional slit-like lumens. Note columnar cells with no or minimal atypia. This tumor exhibited no appreciable papillae

to-back nature of the proliferation and evidence of local invasion. By immunohistochemistry, the cells are CK7 positive, but are CK20 and CDX-2 negative. S100 may be positive in some tumors. The lack of basal cells is confirmed by an absence of p63 or 34BE12 staining [32, 33], although p63 positivity in a rare tumor has been reported [34].

Treatment and Prognosis

The treatment is complete surgical excision, with or without radiation depending on the extent of disease and adequacy of resection. The prognosis is good, with limited recurrences and rare metastases or deaths from disease. Combining the case series in the literature, the overall recurrence rate is 26 %. The true figure may actually be lower, as the pathological definition of LGNIA has been refined since the early papers, possibly excluding some salivary type or high grade tumors that had been classified as LGNIA [31, 32].

Differential Diagnosis

The differential diagnosis is with other adenocarcinomas (including metastatic carcinoma) and with seromucinous hamartoma. Comprehensive discussion of this topic is beyond the scope of this article. Salivary type adenocarcinomas of the nose resemble those in other locations, but there can be considerable overlap of low-grade types with LGNIA. One relevant note is that while occasional LGNIA may contain intracytoplasmic zymogen granules, it does not have the architectural patterns or cytological diversity (acinar cells, clear cells, canalicular cells) of conventional acinic cell carcinoma.

In contrast to SMH, the glands in LGNIA are closely packed and back-to-back, at least in significant areas. Infiltrative borders may be noted if sufficient tissue is received. SMH has more loosely-packed glands that often bud from and surround larger ciliated glands, sometimes with a lobular growth pattern. SMH also has a greater amount of intervening stroma. The architecture of LGNIA is more variable than SMH, and may include papillae and pseudostratification. The immunoprofile of the two entities is similar, except for the more uniform and consistent expression of S100 in SMH.

The distinction between SMH and LGNIA is open to interpretation and the biases of individual pathologists [33]. This is a particularly problematic distinction in light of the low rates of recurrence and metastases for LGNIA and the rarity of both conditions, with little opportunity for long-term follow-up of a large series of cases. One should be cautious about diagnosing LGNIA in combination with REAH. Back-to-back architecture in which gland

formation is attenuated (Fig. 10a), the presence of papillae, pseudostratification, S100 negativity, or any mitotic activity should lead to a high suspicion of malignancy.

Finally, rare cases of sclerosing polycystic adenosis (SPA) have been reported in the nasal cavity [35, 36]. SPA is an uncommon, benign, tumefactive salivary gland condition that resembles fibrocystic disease and/or sclerosing adenosis of the breast. It most commonly affects the parotid, but may affect minor salivary glands as well. The combination of an irregular, sclerotic glandular proliferation with atypia may mimic LGNIA. However, SPA typically maintains a lobular configuration and contains a variety of cell types, including characteristic cells with bright eosinophilic intracytoplasmic globules that are not typical of LGNIA. Unlike LGNIA, SPA maintains a dual cell population, the abluminal component of which can be highlighted with basal/myoepithelial stains such as p63, smooth muscle actin, or calponin.

Conclusions

Low-grade epithelial sinonasal lesions are a small but fascinating group of entities. Schneiderian papillomas are sufficiently well characterized that most can easily be diagnosed on the basis of established criteria. However, malignancies arise in both ISP and OSP, so close evaluation of the biopsy material is required. The precise nature of those lesions designated “hamartomatous” is still poorly understood and requires further study. REAH and SMH are increasingly being found in association with chronic rhinosinusitis and nasal polyposis, suggesting an inflammatory origin. There is limited molecular evidence for a neoplastic origin as of yet. As more is published, these entities will likely be increasingly recognized by general surgical pathologists in routine head and neck material. The distinction between SMH and LGNIA is controversial, although certain features should lead to a diagnosis of malignancy. However, LGNIA, when strictly diagnosed, rarely metastasizes and may be adequately treated by surgical resection alone.

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References

1. Vorasubin N, Vira D, Suh JD, Bhuta S, Wang MB. Schneiderian papillomas: comparative review of exophytic, oncocytic and inverted types. *Am J Rhino Allergy*. 2013;27(4):287–92.
2. Barnes L. Diseases of the nasal cavity, paranasal sinuses and nasopharynx. In: Barnes L, editor. *Surgical pathology of the head*

- and neck. 3rd ed. New York: Informa Healthcare; 2009. p. 343–422.
3. Barnes L, Tse LLY, Hunt JL. Schneiderian papillomas. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. WHO classification of tumors. Pathology and genetics: head and neck tumors. Lyon: IARC Press; 2005. p. 28–32.
 4. Perez-Ordóñez B. Hamartomas, papillomas and adenocarcinomas of the sinonasal tract and nasopharynx. *J Clin Pathol*. 2009;62:1085–95.
 5. Syrjänen KJ. HPV infections in benign and malignant sinonasal lesions. *J Clin Pathol*. 2003;56(3):174–81.
 6. Brandwein M, Steinberg B, Thung S, Biller H, Dilorenzo T, Galli R. Human papillomavirus 6/11 and 16/18 in Schneiderian papillomas. In situ hybridization with human papillomavirus RNA probes. *Cancer*. 1989;63:1708–13.
 7. Buchwald C, Franzmann MB, Jacobsen GK, Juhl BR, Lindeberg H. Carcinomas occurring in papillomas of the nasal system associated with human papillomavirus (HPV). *Rhinology*. 1997;35(2):74–8.
 8. Lawson W, Ho BT, Shaari CM, Biller HF. Inverted papilloma: a report of 112 cases. *Laryngoscope*. 1995;105:282–8.
 9. Anari S, Carrie S. Sinonasal inverted papillomas: narrative review. *J Laryngol Otol*. 2010;124:705–15.
 10. Barnes L. Schneiderian papillomas and nonsalivary glandular neoplasms of the head and neck. *Mod Pathol*. 2002;15:279–97.
 11. Barnes L, Bedette C. Oncocytic Schneiderian papilloma: a reappraisal of cylindrical cell papilloma of the sinonasal tract. *Hum Pathol*. 1984;15:344–51.
 12. Ward BE, Fechner RE, Mills SE. Carcinoma arising in oncocytic Schneiderian papilloma. *Am J Surg Pathol*. 1990;14:364–9.
 13. Maitra A, Baskin LB, Lee EL. Malignancies arising in oncocytic Schneiderian papillomas. A report of 2 cases and review of the literature. *Arch Pathol Lab Med*. 2001;125:1365–7.
 14. Lewis JS Jr, Chernock RD, Haynes W, El-Mofty SK. Low-grade Schneiderian carcinoma, a unique and deceptively bland malignant neoplasm. *Am J Surg Pathol*. 2015;39(5):714–21.
 15. Wenig BM, Heffner DK. Respiratory epithelial adenomatoid hamartomas of the sinonasal tract and nasopharynx: a clinicopathological study of 31 cases. *Ann Otol Rhinol Laryngol*. 1995;104(8):639–45.
 16. Lee JT, Garg R, Brunworth J, Keschner DB, Thompson LDR. Sinonasal respiratory epithelial adenomatoid hamartomas: series of 51 cases and literature review. *Am J Rhinol Allergy*. 2013;27:322–8.
 17. Fitzhugh VA, Mirani N. Respiratory epithelial adenomatoid hamartoma: a review. *Head Neck Pathol*. 2008;2(3):203–8.
 18. Baillie EE, Batsakis JG. Glandular (seromucinous) hamartoma of the nasopharynx. *Oral Surg Oral Med Oral Pathol*. 1974;38(5):760–2.
 19. Fleming KE, Perez-Ordóñez B, Nasser JG, Psooy B, Bullock MJ. Sinonasal seromucinous hamartoma: a review of the literature and a case report with focal myoepithelial cells. *Head Neck Pathol*. 2012;6(3):395–9.
 20. Khan RA, Chernock RA, Lewis JS Jr. Seromucinous hamartoma of the nasal cavity: a report of two cases and review of the literature. *Head Neck Pathol*. 2011;5(3):241–7.
 21. Ambrosini-Spaltro A, Morandi L, Spagnolo DV, Cavazza A, Brisigotti M, Domicini S, Jain S, Eusebi V. Nasal seromucinous hamartoma (microglandular adenosis of the nose): a morphological and molecular study of five cases. *Virchows Arch*. 2010;457(6):727–34.
 22. Weinreb I, Gnepp DR, Laver NM, Hoschar AP, Hunt JL, Seethala RR, Barnes EL, Chetty R, Perez-Ordóñez B. Seromucinous hamartomas: a clinicopathological study of a sinonasal glandular lesion lacking myoepithelial cells. *Histopathology*. 2009;54(2):205–13.
 23. Gauchotte G, Mari B, Gallet P, Nguyen DT, Grandhaye M, Jankowski R, Vignaud J-M. Respiratory epithelial adenomatoid hamartoma: a poorly recognized entity with mast cell recruitment and frequently associated with nasal polyposis. *Am J Surg Pathol*. 2013;37(11):1678–85.
 24. Ozolek JA, Hunt JL. Tumor suppressor gene alterations in respiratory adenomatoid hamartoma (REAH): comparison to sinonasal adenocarcinoma and inflamed sinonasal mucosa. *Am J Surg Pathol*. 2006;30(12):1576–80.
 25. Choi E, Catalano PJ, Chang G. Chondro-osseous respiratory epithelial hamartoma of the sinonasal tract. *Oto-Head Neck Surg*. 2006;134:168–9.
 26. Weinreb I. Low grade glandular lesions of the sinonasal tract: a focused review. *Head Neck Pathol*. 2010;4(1):77–83.
 27. Chuang SS, Lin CN. Microglandular adenosis arising in chronic paranasal sinusitis. *Histopathology*. 2000;36(4):376–7.
 28. Mills SE, Gaffey MJ, Frierson HF. Miscellaneous tumor like lesions. In: Atlas of tumor pathology: tumors of the upper aerodigestive tract and ear. 3rd series. Washington, DC: Armed Forces Institute of Pathology 2000; pp 357–59.
 29. Leivo I. Update on sinonasal adenocarcinoma: classification and advances in immunophenotype and molecular genetic make-up. *Head Neck Pathol*. 2007;1(1):38–43.
 30. Brandwein-Gensler M, Wei S. Envisioning the new WHO head and neck classification. *Head Neck Pathol*. 2014;8:1–15.
 31. Heffner DK, Hyams VJ, Hauck KW, Lingeman C. Low grade adenocarcinoma of the nasal cavity and paranasal sinuses. *Cancer*. 1982;50:312–22.
 32. Mills SE, Gaffey MJ, Frierson HF. Glandular neoplasms. In: Atlas of tumor pathology: tumors of the upper aerodigestive tract and ear. 3rd series. Washington, DC: Armed Forces Institute of Pathology 2000; pp 149–72.
 33. Jo VY, Mills SE, Cathro HP, Carlson DL, Stelow EB. Low grade sinonasal adenocarcinomas: the association with and distinction from respiratory epithelial adenomatoid hamartomas and other glandular lesions. *Am J Surg Pathol*. 2009;33(3):401–8.
 34. Ozolek JA, Barnes EL, Hunt JL. Basal/myoepithelial cells in chronic sinusitis, respiratory epithelial adenomatoid hamartoma, inverted papilloma and intestinal-type and nonintestinal-type sinonasal adenocarcinoma: an immunohistochemical study. *Arch Pathol Lab Med*. 2007;131(4):530–7.
 35. Park I-H, Hong S-M, Choi H, Chang H, Lee H-M. Sclerosing polycystic adenosis of the nasal septum: the risk of misdiagnosis. *Clin Exp Otorhinolaryngol*. 2013;6(2):107–9.
 36. Su A, Bhuta SM, Berke GS, Lai CK. A unique case of sclerosing polycystic adenosis of the sinonasal tract. *Hum Pathol*. 2013;44:1937–40.