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ORIGINAL ARTICLE

Nasal seromucinous hamartoma (microglandular adenosis of the nose): a morphological and molecular study of five cases

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Abstract Five cases of nasal seromucinous hamartoma were studied and their clinical, morphological, immunohistochemical and molecular data are reported. The patients, three females and two males, ranged in age from 49 to 66 years (mean 56 year, SD±7.91). All lesions were located in the nasal cavity. In four cases where follow-up was obtained, no recurrence was evident. In all cases, numerous small seromucinous tubules, embedded in a cellular stroma, were present in the lamina propria. Tubules were lined by one layer of cuboidal cells which displayed luminal phenotype positive for lysozyme and EMA in four, and S100 protein in all cases. Collagen IV and laminin positive basal lamina outlined the tubules which lacked basal cells. Stromal spindle cells present among tubules were immunoreactive for calponin in all cases and for alpha-smooth muscle actin in four cases. DNA mutation analysis of mitochondrial D-loop region was performed by direct sequencing in order to verify the mutation rate of these lesions. The tubules of the five seromucinous hamartomas showed a higher mutation rate especially in heteroplasmy (0.52% homoplasmy, 2.02% heteroplasmy) in comparison to normal seromucinous glands which exhibited a lower mutation frequency (0.83%). This is considered a sign of a low cellular proliferation rate consistent with a benign process. It is concluded that nasal seromucinous hamartomas are benign glandular proliferations that may resemble microglandular adenosis of the breast. Their distinction from benign and malignant mimics is discussed.

Keywords Seromucinous hamartoma · Nasal cavity · Microglandular adenosis

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Introduction

Seromucinous hamartoma (SH) is a rare benign glandular proliferation of the sinonasal tract and nasopharynx which was described by Baillie and Batsakis in 1974 [1]. These authors reported a polypoid mass of the nasopharynx, composed of a lobular arrangement of numerous small seromucinous tubules immersed in cellular connective tissue. Similar lesions were subsequently described as

Table 1 List of all antibodies used

Antigen	Source	Clone
Alpha-SMA	Cell marque	1A4
Calponin	Cell marque	CALP
Desmin	Ventana	DE-R-II
p63	Cell marque	4A4
CK14	Cell marque	LL002
Laminin	Thermo scientific	LMN02 (alias 4C7)
Collagen IV	Cell marque	CIV22
S100	Ventana	4C4.9
Ki67	Ventana	30-9
Lysozyme	Cell marque	Polyclonal
EMA	Cell marque	E29

SMA smooth muscle actin; *S100* protein S100; *EMA* epithelial membrane antigen; *CK14* cytokeratin 14

nasopharyngeal hamartoma [2] and hamartoma of the nose and nasopharynx [3]. Chuang and Lin reported a case in the paranasal sinuses, noticing a close similarity with microglandular adenosis (MGA) of the breast [4].

The aim of the present paper was to study five cases of nasal SH in order to further define the clinical, morphological, immunohistochemical and molecular features of this condition. For molecular analysis, the mitochondrial DNA (mtDNA) mutation rate was specifically studied, as situations of homoplasmy are indicative of malignant lesions, while lesions showing heteroplasmy are more frequently hyperplastic [5].

Materials and methods

Five cases of nasal polyps showing morphological features consistent with SH were collected. Two cases were retrieved from the files of the Section of Anatomic Pathology "Marcello Malpighi" of the University of Bologna. The other three cases were recruited from other institutions (AC, SJ, MB).

All cases were histologically reviewed by two of us (AAS, VE).

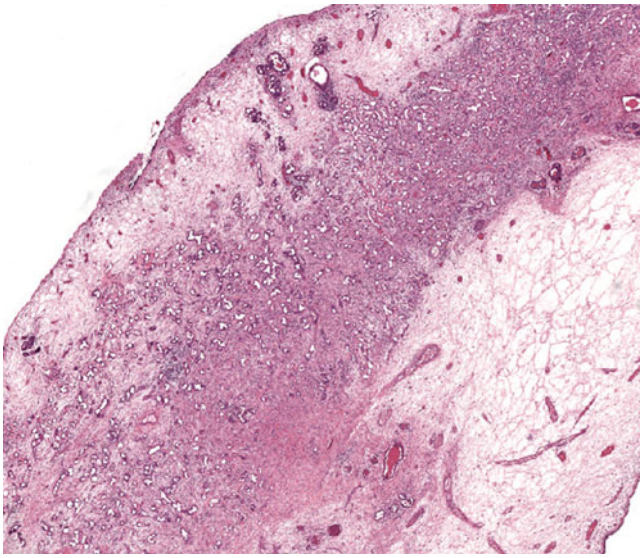

Fig. 1 *Case 3 (H&E).* The seromucinous glands proliferate parallel to the overlying mucosa; the lesional stroma is cellular, in contrast to the stroma of the rest of the polyp which is loosely oedematous. At low power, the lesion may mimic adenocarcinoma

For molecular comparison with SH, normal control nasal turbinate mucosa from five patients of the same age range was retrieved from the histology files. All cases had been fixed in 10% buffered formalin and embedded in paraffin as routine.

Immunohistochemical analysis

Five-micrometre sections of selected blocks from all cases were immunostained using an automated immunostainer (Ventana Medical Systems, Inc, Tucson, Arizona, USA). The antibodies used are listed in Table 1.

Molecular analysis

From each of the five lesional cases, cells from the proliferating seromucinous tubules in the lamina propria and from the overlying respiratory epithelium were selectively microdissected for comparison. Similarly, normal mucosa from the five control cases was also harvested.

Table 2 Clinical features

Case number	Sex	Age	Site	FU	Major axis (cm)
1	M	50	Nasal cavity	A&W, 8 years	3.5
2	F	66	Nasal cavity	A&W, 8 years	3
3	F	63	Nasal cavity	A&W, 7 years	1.5
4	M	49	Nasal cavity (arising from nasal septum)	A&W, 1 year	2.5
5	F	52	Nasal cavity	NA	1

FU follow-up, *A&W* alive and well, *NA* not available

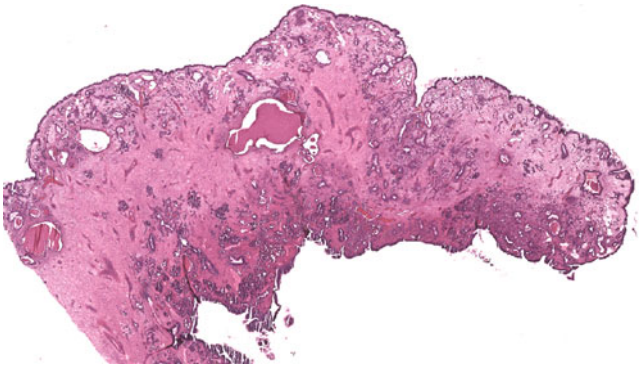

Fig. 2 *Case 4 (H&E).* The polypoid lesion exhibits seromucinous glands distributed along the major axis. Cystically dilated spaces intermixed with the proliferation are evident

Pertinent areas were microdissected using the laser assisted SL μcut Microtest (MMI GmbH Glattbrugg, Switzerland), as previously described [6, 7].

Mitochondrial DNA was extracted using the high pure PCR template kit (Roche, Manheim, Germany) following the manufacturer's instructions.

A negative control, to which no tissue was added, was processed in parallel with each sample to exclude any contamination. MtDNA D-loop sequence analysis was performed by amplifying four overlapping segments of about 300 bp, covering the entire region from position 16,056 to position 729 (see www.mitomap.org for revised Cambridge mtDNA reference sequence). The D-loop region was chosen as it contains hot spots for mtDNA mutation in cancer cells [5, 8–12]. Primers used have been previously described [6]. PCR products were directly sequenced using CEQ2000 XL instrument (Beckman Coulter, Inc., Fullerton, CA, USA) following the manufacturer's instructions. Multiple sequence alignment and mutation rate were calculated using MEGA 4.1 software (Molecular Evolutionary Genetics Analysis, MEGA, The Biodesign Institute, Tempe, AZ, USA).

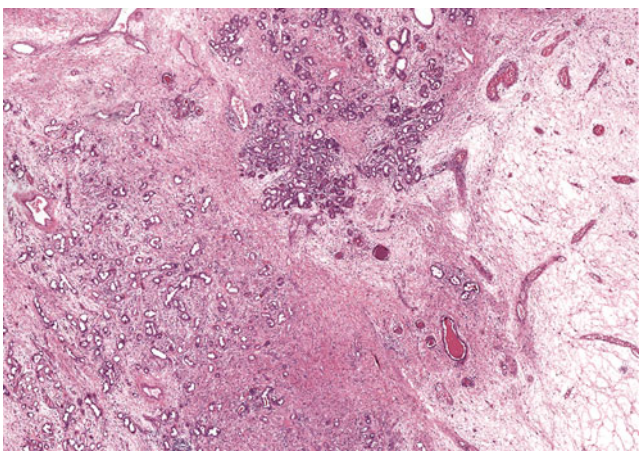

Fig. 3 *Case 3 (H&E).* The proliferating tubules (*left*) are easily distinguished from the normal residual seromucinous glands (*right*)

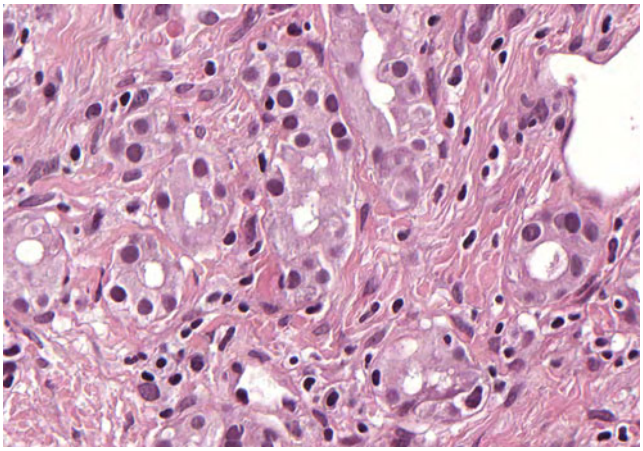

Fig. 4 *Case 1 (H&E).* The tubules are lined by a single layer of cuboidal epithelium, with amphophilic to eosinophilic cytoplasm and regular, monomorphic nuclei

Results

Clinical features

Clinical features are summarised in Table 2. There were three females and two males, with ages ranging from 49 to 66 years (mean 56 year, SD±7.91). All the lesions were polyps in the nasal cavity. In case 4, the lesion arose from the nasal septum.

Follow-up available in four of the five cases ranged from 1 to 8 years (mean 6 years, SD±3.4). All patients are alive and well, with no nasal symptoms.

Histological features

The histological features are similar in all cases and will be described together. All lesions were polypoid and consisted of a proliferation of small tubules of the same size as pre-existing normal acini located in the lamina propria. The

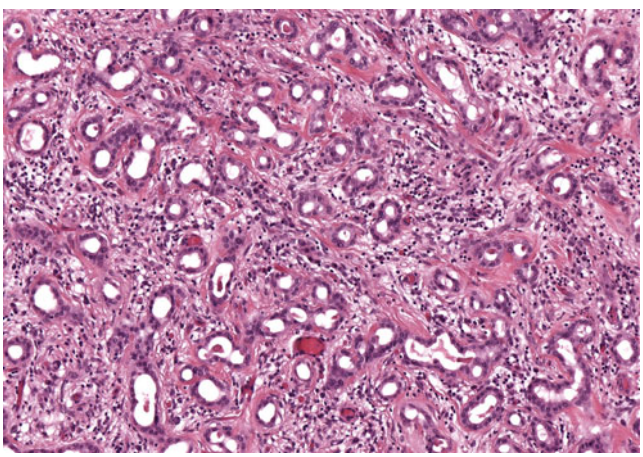

Fig. 5 *Case 3 (H&E).* The tubules are encircled by a thick basal lamina

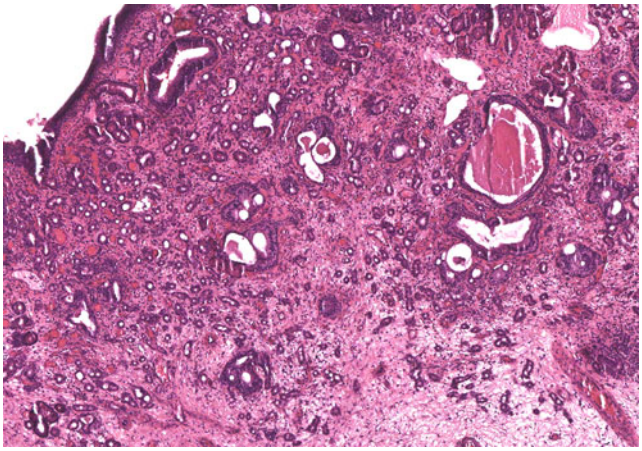

Fig. 6 *Case 4 (H&E).* Tubules are admixed with invaginations of superficial epithelium into the lamina propria, forming small cysts lined by respiratory epithelium

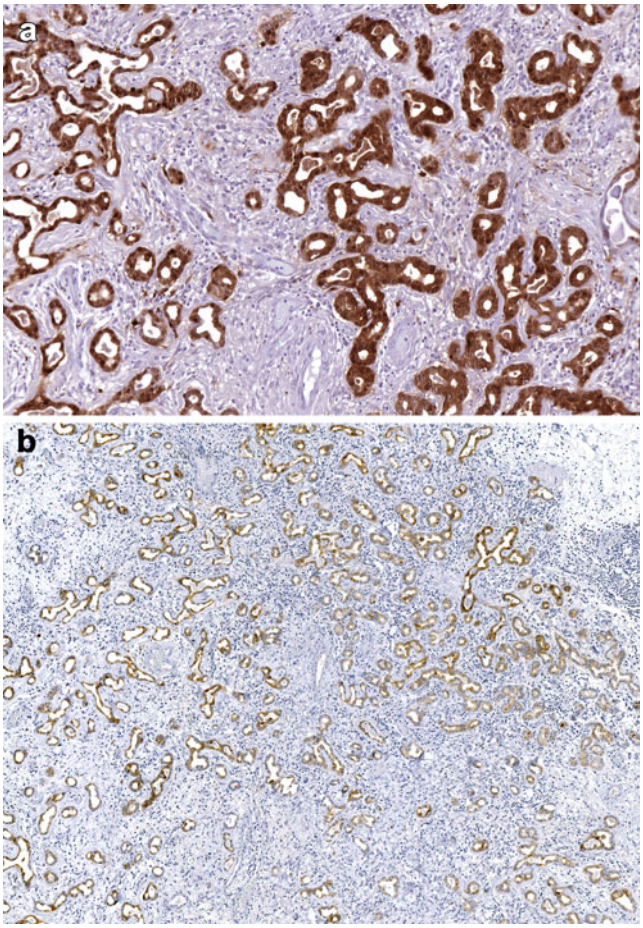

Fig. 7 The tubules are diffusely and strongly immunoreactive for protein S100 (**a**, case 3) and for EMA (**b**, case 3)

tubules proliferated mostly in a laminar fashion beneath and parallel to overlying respiratory epithelium (Figs. 1, 2). Tubules were intermingled with and of the same size of pre-existing acini (Fig. 3). The tubules were composed of a single layer of cuboidal epithelium exhibiting little variation in size and shape. The cytoplasm varied from amphophilic to eosinophilic; occasional mucinous goblet cells were observed. Nuclei were round to ovoid with little variation in size (Fig. 4). Mitoses were absent. Eosinophilic secretion was occasionally present within the lumina of the tubules. The tubules were encircled by thick eosinophilic basal lamina (Fig. 5). The stroma present among the tubules was composed of numerous spindle cells, contrasting with the oedematous loose stroma of the non-lesional part of the polyps and in addition contained mild chronic inflammatory infiltrate composed chiefly of small lymphocytes (Fig. 5).

In all cases, invaginations into the lamina propria by the superficial respiratory ciliated epithelium resulted in the formation of small cysts (Fig. 6). In case 2, the proliferation of the native respiratory epithelium was so exuberant as to mimic the features of a respiratory epithelial adenomatoid hamartoma (REAH), admixed with the tubular proliferation [13–17].

Table 3 Immunohistochemical features

Number	SMA (stroma)		Calponin (stroma)		Desmin (stroma)		p63		CK14		Laminin		Coll IV		S100		Ki67		Lysozyme		EMA	
	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R
1	−	−	+	+	−	−	−	+	−	−	−	−	+	+	+	−	1%	2%	+	foc+	+	foc+
2	foc+	foc+	+	+	−	−	−	+	−	−	+	+	+	+	foc+	−	1%	2%	+	foc+	foc+	foc+
3	+	+	+	−	foc+	−	−	+	−	−	−	−	+	+	+	−	1%	1%	+	foc+	+	+
4	+	+	+	+	−	−	−	+	−	−	−	+	+	−	+	−	1%	2%	−	foc+	foc+	foc+
5	+	+	+	+	foc+	foc+	−	+	−	−	foc+	−	+	+	foc+	−	2%	5%	foc+	foc+	−	foc+

N case number; *SMA* smooth muscle actin; *CK14* cytokeratin 14; *Coll IV* collagen IV; *S100* S100 protein; *EMA* epithelial membrane antigen; + positive; − negative; *foc+* focally positive; *S* seromucinous component; *R* respiratory epithelium (superficial and invaginated)

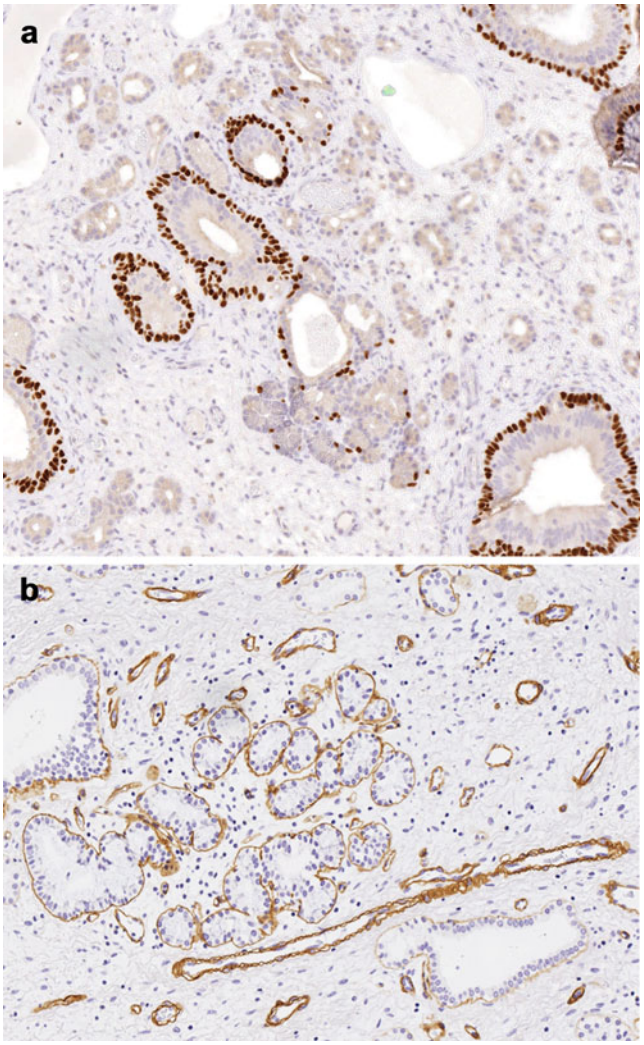

Fig. 8 Basal cells reactive for p63 are detected only around invaginated respiratory epithelium and are absent around proliferating seromucinous tubules (**a**, case 4), which are instead decorated by laminin positive basal lamina (**b**, case 2)

The five cases of normal turbinate mucosa selected for genetic analysis showed normal acinar glands regularly distributed in the lamina propria.

Immunohistochemical features

All immunohistochemical features are summarised in Table 3.

Tubules

The cytoplasm of the cuboidal cells lining the tubules was positive for S100 protein in all cases (Fig. 7a) and for lysozyme and EMA (Fig. 7b) in four. Virtually, all tubules were devoid of basal cells, as seen by the lack of p63 (Fig. 8a) and CK 14 positive elements and were outlined by basal lamina positive for laminin in two cases (cases 2 and 5; Fig. 8b) and for collagen IV in all cases.

The tubular epithelial cells had a proliferation index of 1–2% (Ki67).

Respiratory epithelium and residual acinar glands from both lesional and normal tissues

Respiratory epithelium was negative for S100 protein in all cases, while it exhibited positivity for EMA and focal immunoreactivity for lysozyme in all cases. Basal cells positive for p63 were consistently present in all cases (Fig. 8a), but CK14 immunoreactivity was not seen. Laminin positive basal lamina was observed in two cases

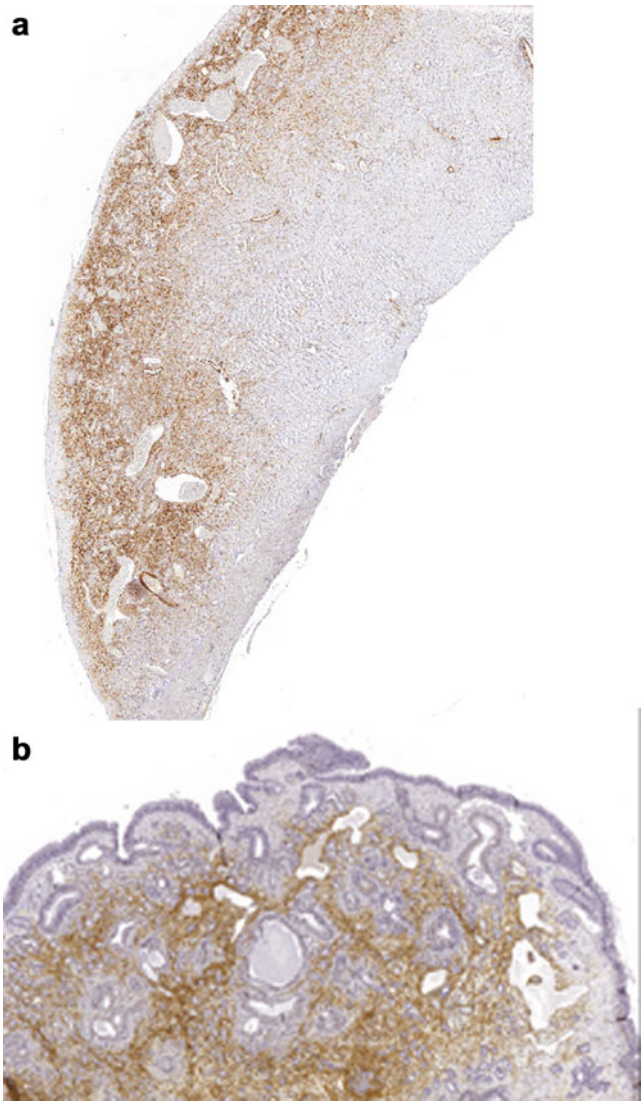

Fig. 9 The cellular stroma around the proliferating tubules is reactive for both calponin (**a**, case 1) and SMA (**b**, case 4)

Table 4 Molecular features

Number	Homoplasmy	Heteroplasmy	Total
Lesional cases			
1	0.87	3.42	4.30
2	0.26	1.39	1.65
3	0.69	2.00	2.69
4	0.77	1.93	2.7
5	0	1.34	1.34
Mean	0.52	2.02	2.50
Normal cases			
1	0	1.00	1.04
2	0	0.62	0.62
3	0.19	0.38	0.57
4	0.77	0.77	1.55
5	0.19	0.57	0.76
Mean	0.23	0.67	0.83

The percentages indicate mutation frequency in mitochondrial DNA, as detected by the comparison between seromucinous tubules, normal glands and superficial respiratory epithelium

(cases 2 and 4) and collagen IV immunoreactivity was found in four cases (cases 1, 2, 3 and 5).

The residual normal seromucinous glands, observed in four cases (cases 1–4), were encircled by basal cells expressing both p63 and CK14. In these four cases, the residual glands also showed the presence of a laminin- and collagen IV-positive basal lamina.

Stroma

The cellular stroma in which the tubules were embedded exhibited immunoreactivity for calponin in all cases (Fig. 9a), for smooth muscle actin (SMA) in four cases (Fig. 9b) and for desmin in two cases.

The stroma elsewhere in the polyps, and in the adjacent normal nasal tissues, was negative for calponin, SMA and desmin.

Table 6 Summary of the similarities and differences between seromucinous hamartoma of the nose and microglandular adenosis of the breast

	SH of the nose	MGA of the breast
Similarities		
Small proliferating tubules	Present	Present
Secretion in the lumina	Eosinophilic	Eosinophilic
S100 protein immunoreactivity of luminal cells	Positive	Positive
Basal (myoepithelial) cells	Absent	Absent
Basal lamina	Present	Present
Differences		
EMA immunoreactivity of luminal cells	Positive	Negative
Lesional stroma	Cellular	Fibrofatty

SH seromucinous hamartoma, *MGA* microglandular adenosis

Molecular features

The seromucinous glands of the five cases of normal nasal mucosa exhibited a mtDNA mutation rate of 0.83% (0.23% homoplasmy, 0.67% heteroplasmy).

The tubules of the five SH cases had a higher (2.50%) mtDNA mutation rate, especially in heteroplasmy (0.52% homoplasmy, 2.02% heteroplasmy, see Table 4 for details).

Table 5 Summary of the previously reported seromucinous hamartoma (microglandular adenosis) of the nose and paranasal sites

Authors, Ref.	Number of reported lesions	Original diagnosis	Sex	Age	Site	FU
Baillie et al. [1]	1	Glandular (seromucinous) hamartoma of the nasopharynx	M	26	Nasopharynx, attached to the posterior vomer	A&W, 2 1/2 years
Zarbo et al. [2]	1	Nasopharyngeal hamartoma	M	32	Nasopharynx	A&W, 2 years
Graeme-Cook et al. [3]	1	Hamartoma	F	57	Posterosuperior left nasal cavity	A&W, 1 year
	2	Hamartoma	F	67	Posterior left nasal cavity	A&W, 10 months
	3	Hamartoma	F	78	Nasopharyngeal mass	A&W, 4 months
Chuang et al. [4]	1	Microglandular adenosis	M	54	Paranasal sinus	A&W, 6 months
Weinreb et al. [18]	7[a]	Seromucinous hamartoma	4M, 3F	14–85	Nasal cavity	4 A&W, 1 rec, 6 months to 5 years

A&W alive and well, *rec* recurrence

[a] Cases are collectively described

Discussion

Seromucinous hamartoma is a rare lesion of the nasal cavity which may cause nasal obstruction and breathing difficulties. The polypoid lesion attached to the posterior vomer and expanding in the soft palate described by Baillie and Batsakis [1], that they named glandular (seromucinous) hamartoma, is very similar to the present cases. The lesions subsequently reported (with varying nomenclature) by Zarbo et al. [2], Graeme-Cook et al. [3], Chuang et al. [4] and Weinreb et al. [18] (Table 5) are also similar.

Our cases showed proliferating tubules closely simulating an invasive low-grade adenocarcinoma. Nevertheless, the organoid pattern of growth with parallel spread under and along the surface epithelium, the lack of cytologic atypia and mitoses, the presence of collagen IV and laminin positive basal lamina around the tubules together with lack of recurrences in the four cases where follow-up was available, are all features indicating a benign glandular proliferation. Chuang and Lin [4] suggested close similarity of their case to MGA of the breast, a rare benign lesion which may also simulate invasive carcinoma [19–22].

If our five cases are compared with previously reported MGA of the breast [23], both similarities and differences are evident. Both lesions are characterised by small proliferating tubules, presence of eosinophilic secretion in the lumina, S100 protein positivity of luminal cells, lack of basal (myoepithelial) cells and presence of basal lamina. In spite of these similarities, there are consistent differences. In MGA of the breast, the proliferating cells are EMA negative and are immersed in fibrofatty stroma [23]. By contrast, the cells of our SH cases were clearly EMA positive and were immersed in a cellular stroma (Table 6).

The present cases also differ from pure REAH [13–17, 24], composed of glands lined almost exclusively by ciliated respiratory epithelium, although cases of mixed REAH and seromucinous hamartomas were described by Weinreb et al., suggesting the existence of a possible spectrum between the two lesions [18, 25]. In the present cases, invaginated respiratory epithelium was identified in all cases (and particularly in case 2), thus confirming the possibility of overlapping features between the two hamartomatous proliferations.

Jo et al. reported an association with REAH in 6/29 cases of sinonasal adenocarcinomas, with a similar immunohistochemical profile, suggesting that REAHs may also be related to adenocarcinomas [26].

The genetic alterations here studied in SH documented an increased mtDNA mutation rate, especially heteroplasmic, in the seromucinous proliferation in contrast to the five normal cases. This favours the view that the number of divisions seen in these lesions was not enough to produce the homoplasmic condition, typical of malignant lesions [5, 27].

Most of the somatic mutations found in mtDNA cancer cells are homoplasmic (i.e. all mitochondria share the same mutation), while fewer cells have heteroplasmic mutations (i.e. a mixture of wild type and mutant mtDNA) [5, 10–12, 27]. Accordingly, mtDNA D-loop homoplasmic mutations were recently shown to be present in poorly differentiated hepatocellular carcinoma [8], in non-small cell lung cancer [9, 28], in colorectal cancer [10] and in breast cancer [11]. On the contrary, Park et al. evidenced an increased level of heteroplasmic mtDNA mutations in benign nasal polyps [12].

By computer simulation, Coller and co-workers showed that random drift alone, following the rules of population genetics, can explain how tumours can accumulate mtDNA variants that cannot be found in normal tissues of the patient, even if these variants are functionally neutral providing no advantage to cancer cells [5].

Taking into account the benign clinical behaviour, the absence of morphological features of malignancy and the presence of mtDNA mutations in heteroplasmy, it can be concluded that this uncommon nasal tubular proliferation has to be regarded a benign nasal lesion.

Conflict of interest statement We declare that we have no conflict of interest.

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