Respiratory epithelial adenomatoid hamartoma of the nose: An updated review

Duc Trung Nguyen, M.D., Ph.D.,[1] Guillaume Gauchotte, M.D., Ph.D.,[2] Fabien Arous, M.D.,[3] Jean-Michel Vignaud, M.D., Ph.D.,[2] and Roger Jankowski, M.D., Ph.D.[1]

ABSTRACT

Background: *This study was designed to update clinical and imaging features as well as treatment outcomes of the nasal respiratory epithelial adenomatoid hamartoma (REAH). Data sources included case reports, original articles, and reviews published in English or French in PubMed from 1995 to date.*

Methods: *Only published articles that met Wenig's histological criteria for the diagnosis of REAH were included.*

Results: *REAH is not rare and is probably underdiagnosed. It is usually observed in the fifth decade of life with a 3:2 male/female predilection. REAH can be represented in two forms: as an isolated lesion (less frequent) or in association with an inflammatory process (especially nasal polyposis). It was observed in 35–48% of patients undergoing endoscopic endonasal surgery for nasal polyposis. Its origin is found, in most cases, in the olfactory cleft, which is exhibited on computed tomography (CT) scans by widened opacified olfactory clefts without bone erosion. Resection of REAH from the olfactory clefts does not worsen, but instead, can improve the sense of smell after surgery.*

Conclusion: *Looking for REAH on CT scans and during endoscopic examination can lead to its diagnosis and help avoid aggressive surgical procedures and their complications. Endoscopic resection is the treatment of choice. The removal of REAH constitutes a specific surgery on the olfactory clefts, which can improve nasal obstruction as well as sense of smell. Whether REAH can be defined as a hamartoma, an inflammatory reactive process, or a neoplastic lesion remains to be determined.*

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The term "hamartoma" was first used to describe nonneoplastic malformations or inborn errors of tissue development constituted by a mixture of tissue.[1] In 1995, Wenig and Heffner used the term "respiratory epithelial adenomatoid hamartoma" (REAH) to describe what they considered a benign neoplasm found in the nose and sinus cavities.[2] REAH was described as "a proliferation of glands lined by multilayered ciliated respiratory epithelium, often with admixed mucocytes, arising in direct continuity with the surface epithelium, which invaginate downward into the submucosa."[2] It was suspected that REAH was being misdiagnosed as other benign or malignant lesions, including inflammatory polyp, inverted papilloma, sinonasal adenocarcinoma, olfactory neuroblastoma, *etc.* Four distinct histopathological hamartomas have been distinguished in the sinonasal tract: congenital hamartoma,[3] sinonasal seromucinous hamartoma,[4–7] mesenchymal hamartoma[8] and its subtype (chondro-osseous respiratory epithelial hamartoma),[9–13] and REAH.[2,14] However, this article focuses solely on REAH.

Until recently, literature regarding REAH has been primarily limited to case reports (Table 1), which include two seminal studies: one that first described REAH in the nose and sinus cavities[2] and one that first reported the origin of REAH in the olfactory clefts.[15] REAH can be observed in two forms: isolated REAH (less frequent) or in association with another inflammatory process (most commonly, nasal polyposis [NP]).[2,16–25] REAH was found in ~35–48% of patients operated on for NP.[18,23,24] This entity, which has been considered as a rare lesion, is, in fact, underdiagnosed. The high rate of REAH now observed can be explained by (i) a systematic checkup of the olfactory clefts on any sinonasal CT scan and during endoscopic surgery, (ii) a systematic individualization of the surgical specimens removed from the olfactory clefts and from the ethmoidal labyrinths for pathological processing, and (iii) highly experienced pathologists with great knowledge of REAH's histological features since 2003.

Accurate recognition of REAH before surgery, especially in the isolated form, may avoid overly aggressive and unnecessary surgical procedures and their complications. Moreover, pathologists have to recognize the microscopic features of REAH to avoid a misinterpretation of these lesions with a malignant neoplasm. The aim of this article is to update the clinical and imaging features of the REAH of the nose as well as the outcomes after endoscopic resection.

MATERIALS AND METHODS

An electronic systematic research of case reports, original articles, and reviews in English or in French, published from 1995 to date, was conducted. A search strategy was used with the key word "respiratory epithelial adenomatoid hamartoma" in PubMed and other additional sources. The date of the last electronic search was November 30, 2013. Only published articles with a histological diagnosis of REAH, according to Wenig's definition, were included.

CLINICAL FEATURES

REAH is observed from the third to ninth decade of life with predominance in the fifth decade.[2,18,22,24,25] Predominance of this entity in males was repeatedly reported in several case reports based on Wenig and Heffner's series, which included 27 men and 4 women.[2] In the 394 cases of REAH published as case reports or case series (Table 1), the gender was indicated for 325 patients, which included 199 male and 126 female subjects with a male/female ratio of 3:2. The close association between REAH and NP, with a recognized predominance in male subjects, may explain the difference in the male/female ratio.

Patients with REAH exhibit similar symptoms to those with chronic nasal inflammatory diseases, such as nasal obstruction, nasal discharge, facial pain, facial pressure, headaches, olfactory impairment, or loss (Table 1). Sinonasal symptoms can be experienced for a few months to up to 20 years.[2,15,24] Isolated REAH seemed to be accompanied by a lesser disease burden and fewer symptoms than those of associated REAH.[21] In isolated form, REAH may be misdiagnosed either with NP or a tumor, such as a primary neoplasm of the sinonasal cavity or olfactory neuroblastoma.[26,27] A close relationship between REAH of olfactory clefts and the loss of smell, which did not seem to improve after general steroid treatments, was shown in

from the [1]Department of Ear, Nose, and Throat–Head and Neck Surgery, University Hospital of Nancy, University of Lorraine, Nancy, France, [2]Department of Pathology, University Hospital of Nancy, INSERM U954, University of Lorraine, Nancy, France, and [3]Faculty of Medicine, University of Lorraine, Nancy, France

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Address correspondence to Duc Trung Nguyen, M.D., Ph.D., Service d'Otorhinolaryngologie et Chirurgie Cervico-Faciale, Hôpital Central, Centre Hospitalier Universitaire de Nancy, Hôpital Brabois, rue du Morvan, 54511 Vandoeuvre-les-Nancy Cedex, France
E-mail address: ductrung96@yahoo.com

Table 1 **Literature summary of REAHs**

Authors	No. of Cases	Sites of REAH	Age (yr)	Gender	Nasal Diseases	Duration of Symptoms	Presentation	Follow-up Period
Wenig and Heffner[2] (time period: 1988–1994)	31	Posterior septum, lateral wall, middle meatus, inferior turbinate, nasopharynx, ethmoidal, or frontal sinus,	27–81 (mean age: 58)	4F 27 M	—	Several months up to 8 yr	NO, nasal stuffiness, deviated septum, epistaxis, and chronic rhinosinusitis	4 mo to 5 yr without recurrence
Endo[17]	1	Inferior turbinate	65	M	—	—	Left NO and protrusion into the hard palate	2 yr without recurrence
Himi[38]	1	Maxillary sinus	56	M	—	—	—	1 yr without recurrence
Delbrouck[16]	1	Lateral nasal wall and behind the middle turbinate	79	F	—	—	Left NO, posterior rhinorrhea, and hyposmia	—
Kessler[39]	1	Left maxillary sinus	47	F	—	8 yr	Radiolucency spotted	
Malinvaud[40]	1	Unilateral ethmoid sinus	74	M	—	Several years	NO and epistaxis	3 mo without recurrence
Athre[41]	1	Right frontal sinus	66	F	—	9 mo	Proptosis, dystopia, and frontal headache	—
Metselaar[42]	1	Nasopharynx	68	F	—		NO	13 mo without recurrence
Lima[15]	15	Olfactory clefts	38–83 (mean age: 57)	8 M and 7 F	—	2–20 yr	NO and hypoanosmia	—
Di Carlo[43]	1	Left maxillary sinus	62	M	—	>3 yr	Cacosmia and posterior rhinorrhea	10 mo without recurrence
Ingram[44]	1	Left maxillary sinus	54	M	—	2 yr	NO and left facial pain	—
Roffman[13]	2 (+1)	Middle turbinate;	56; 80	F	—	6 yr	NO and hyposmia	3 mo without recurrence
Georgel[19]	10	Olfactory clefts	52–93 (mean age: 71.9)	6 F and 4 M	—	2–20 yr	NO, dysosmia, rhinorrhea, and facial pain	2.5 yr (8 mo to 7 yr) without recurrence
Liang[45]	1	Nasal cavity	70	M	NP	>10 mo	NO, anosmia, and nasal stuffiness	—
Mortuaire[46]	1 (+1)	Right posterior septum	64	1 F	—	1 mo	NO and swallowing difficulties	—
Picciotti[32]	1	"mass occupying the ethmoid and the ostiomeatal complex bilaterally"	52	M	—		Bilateral NO, anterior discharge, hyposmia, and headache and facial pain	12 mo without recurrence
Seol[27]	1	Olfactory clefts	60	F	Environmental allergies and chronic sinusitis	2 wk	Headache, nasal congestion, altered sense of smell, and stuffiness in both ears	—
Cao[31]	3	Olfactory clefts	50; 46; 51	2 F and 1 M	NP	2 yr	NO, rhinorrhea, and and facial pain	—
Vira[25] (time period: 2000–2011)	54	Sinus contents (46) and nasal cavity (8)	Mean age: 52	31 M and 23 F	Chronic nasal diseases	—	NO, hyposmia, and headache and facial pain	3.8 yr with two recurrences
Eloy[26]	1	Bilateral olfactory clefts	71	M			Right-sided epistaxis	
Lorentz[23] (time period: 2003–2008)	69	Olfactory clefts	—	—	NP	>1 yr	NO, anterior and posterior discharge, and hypoanosmia	—
Braun[30]	6	Anterior and middle part of the olfactory clefts	53	3 M and 3 F	NP	—	NO and dysosmia	>1 yr without recurrence
Hawley[21] (time period: 2006–2011)	45	Olfactory clefts septum and middle turbinates	23–83 (mean age: 55.9)	26 M and 19 F	79% of cases with NP	—	NO, rhinorrhea, and dysosmia	—
Nguyen[24] (time period: Sept 2009- Nov 2010)	32	Olfactory clefts	Mean age: 49.8	13 M and 19 F	NP	17 ± 11.3 yr	NO, anterior and posterior discharge, hypoanosmia, and facial pain	>7 mo without recurrence

Table 1 **Continued**

Authors	No. of Cases	Sites of REAH	Age (yr)	Gender	Nasal Diseases	Duration of Symptoms	Presentation	Follow-up Period
Park[8]	2	Posterior septum bilateral middle meatus	50, 23	F M	NP	3 yr 10 yr	Left NO and NO	1 yr without recurrence
Lee[22]	51	Olfactory clefts and posterior nasal cavity	Mean age: 58.4	37 M and 14 F	68.6% of cases associated with concurrent inflammatory disease	—	Headache, NO, rhinorrhea, hyposmia, and epistaxis	27.2 mo without recurrence
Gauchotte[18] (time period: January 2007–June 2008)	53 19	Olfactory clefts Olfactory clefts	Mean age: 55 Mean age: 59	36 M, 17 F, 9 M, and 10 F	In association with NP solitary REAH	—	—	24 mo with one recurrence

REAH = respiratory epithelial adenomatoid hamartoma; NP = c nasal polyposis; M = male; F = female; NO = nasal obstruction.

Figure 1. *Respiratory epithelial adenomatoid hamartoma (REAH) endoscopic feature (1): a cerebriform, fleshy to firm, pinkish mass of the left olfactory cleft was found after lateralization of the left middle turbinate (2). The REAH is located between the middle turbinate (2) and the nasal septum (3).*

patients with NP.[24] REAH was highly associated with a long duration of NP disease, asthma, and history of repeated sinus surgery.[24] REAH has also been observed in other clinical settings, such as adenoiditis, hereditary hemorrhagic telangiectasia, inverted papilloma, and malignancy.[21,28,29]

Endoscopy usually reveals bilateral (72% in NP-associated form and 79% in isolated form),[18] often asymmetrical or unilateral nasal masses[21–23] of varying sizes, with a slight cerebriform aspect, fleshy to firm, pinkish or sometimes yellowish (Fig. 1). In isolated REAH, the mass typically emerges from the cleft between the nasal septum and the middle turbinates. In NP-associated REAH, the endoscopic diagnosis is more difficult, because inflammatory polyps can also be observed in the olfactory clefts.[23,24]

REAH has been reported to stem from different sites of the sinonasal cavities (Table 1). Of those, the olfactory cleft is the frequent site where REAH develops.[15,23,24] Before 2006, no case of REAH originating in the olfactory clefts had been published. After 2006, many articles that focused on REAH in the olfactory clefts were published.[20,23,24,27,30,31] In some articles,[13,25,32] the precise site of origin of REAH was not clearly described but the widened opacified olfactory cleft on CT/magnetic resonance imaging (MRI) suggests it as the potential origin.

IMAGING FINDINGS

Radiologically, REAH presents itself as a nonenhancing homogenous mass on CT scans that can mimic other benign or malignant lesions. However, REAH is generally not associated with skull base defects or erosions, in contrast with malignant lesions. The widening of the olfactory clefts (width of both olfactory clefts, >10–12 mm) on CT scans, in axial and coronal planes, without bone lysis of the cribriform plate, nasal septum, conchal lamina, and turbinate wall of the ethmoidal labyrinth should increase suspicion of REAH (Fig. 2).[15,20] In isolated REAH, opacities may be observed only in the olfactory clefts that are widened, in contrast to the ethmoidal labyrinth and paranasal sinuses, which are free of opacities. However, REAH can lead to retention of secretion and/or edema in the ethmoidal labyrinth or paranasal sinuses, which can sometimes appear more or less opacified. In some patients, the ethmoid and sinus opacities can completely disappear after a short systemic steroid treatment, leaving only the typical CT scan presentation of the REAH in the olfactory clefts.[23] In

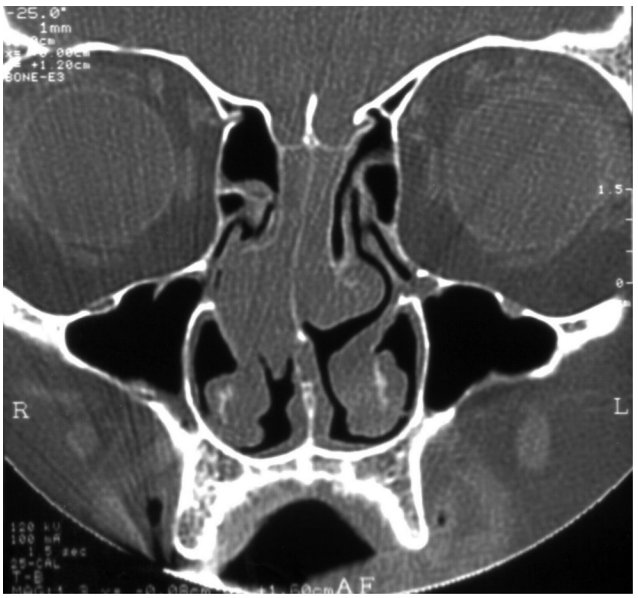

Figure 2. *Computed tomography (CT) scan shows opacified and widened olfactory clefts without bone erosion. Both ethmoidal labyrinths are well ventilated. The endoscopic feature shows a cerebriform, fleshy to firm, pinkish mass of the olfactory clefts (see Fig. 1). These elements suggested an isolated, bilateral respiratory epithelial adenomatoid hamartoma (REAH) in the olfactory clefts. Biopsies were performed and revealed the diagnosis of REAH (see Figs. 3 and 4). A conservative endoscopic surgery without complication was performed. Magnetic resonance imaging (MRI) was not necessary in this typical case.*

NP-associated form, there is opacified widening of the olfactory clefts associated with bilateral opacities of the ethmoidal labyrinths. Sometimes, only endoscopic surgery can make the difference between REAH associated with NP and REAH merely associated with ethmoidal retention.

MRI helps to make the differential diagnosis for unilateral or isolated forms of REAH with meningoencephalocele, inverted papilloma, or malignancy. In such cases, MRI findings allow evaluation of the entire region of the olfactory clefts and contiguous structures. MRI shows clearly delineated cerebriform filling on T2-weighted images and homogenous enhancements on T1-weighted contrast-enhanced sequences.[30] In addition, MRIs help to distinguish REAH from mucus retention in the contiguous paranasal cavities.

PATHOLOGICAL FINDINGS

Histological Features

The diagnosis is usually easy with microscopic examination. The histopathological feature is dominated by a pseudoglandular proliferation with a polypoid appearance.[14,33] These widely spaced, small to medium-sized pseudoglands, which invaginate downward into the submucosa and are separated by stroma tissue, arise in direct continuity at the surface of the epithelium (Fig. 3). The glands are round to oval and are composed of multilayered ciliated respiratory epithelium often with admixed mucocytes (Fig. 4).[14] The stroma is edematous or fibrous and contains a mixed chronic inflammatory cell infiltrate. Other histological findings may include inflammatory nasal polyps, hyperplasia, and/or squamous metaplasia of the surface epithelium unrelated to the adenomatoid proliferation.

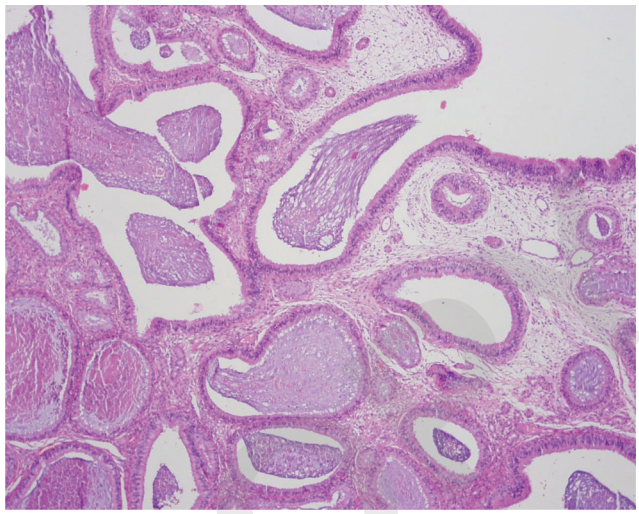

Figure 3. *Respiratory epithelial adenomatoid hamartoma (REAH). Submucosal adenomatoid proliferation takes origin from surface epithelium. These widely spaced, small to medium-sized pseudoglands, which invaginate downward into the submucosa and are separated by stroma tissue, arise in direct continuity at the surface of the epithelium (hematoxylin and eosin, ×4).*

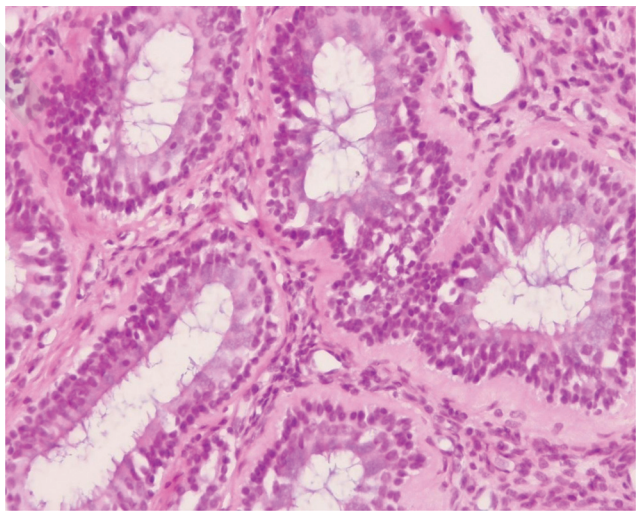

Figure 4. *Adenomatoid proliferation composed of pseudostratified ciliated respiratory epithelium surrounded by hyalinized stroma (hematoxylin and eosin, ×20).*

Immunohistochemistry

Immunohistochemical studies have currently no usefulness in the diagnosis of REAH[33] because there is still no specific immunohistochemical feature to identify REAH.[17]

In 2002, Endo *et al.* reported in one case that <1% of the ductal cells of REAH were positive for MIB-1 and thought that staining with MIB-1 might help to distinguish REAH from neoplasms, which tend to have a high proliferation index.[17] However, it is difficult to draw conclusions from only one observation. Ozolex *et al.*[34] used an immunohistochemical panel including cytokeratin (CK) 7, CK20, 34βE12, CDX-2, p63, KI-67 (MIB-1), smooth muscle actin, S-100 protein, and calponin to examine the profile of REAH and other diseases (chronic sinusitis, inverted papilloma, and intestinal-type and nonintestinal-type sinonasal adenocarcinoma). They showed that only basal cells

were positive for p63 and 34 βE12 in chronic sinusitis and REAH, whereas all of the inverted papillomas stained diffusely positive for these markers. REAH, inverted papilloma, chronic sinusitis, and most sinonasal adenocarcinoma expressed CK7, whereas CK20 and CDX-2 were only seen in most intestinal-type sinonasal adenocarcinoma, and not in REAH or inverted papilloma. Thus, the question was whether this expression is related to the pathogenesis or a mere association with the cellular phenotypes of these lesions. Hence, this staining pattern may prove invaluable in the differential diagnosis of REAH and does not tell anymore about pathogeny.[33]

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of REAH are still unknown. The frequent association between REAH and NP (in 57% of REAH)[21] suggests it is a tumor induced by chronic inflammation, and develops, specifically, from the mucosa of the olfactory clefts.[23,24] It has been argued that the nose can be considered as an assemblage of three different organs—an olfactory nose, a respiratory nose, and the paranasal sinuses—and that specific diseases are related to the compartmentalization of the nose.[35]

Ozolex and Hunt found a high loss of heterozygosity of the loci located on chromosomes 9p and 18q as well as an intermediate fractional allelic loss of 31% in REAH lesions.[36] They concluded that the molecular profile of REAH would be considered unusually high for a nonneoplastic entity, suggesting the possibility that REAH may be a benign neoplasm rather than a hamartoma. However, the microscopic examination of REAH shows a proliferation of multilayered ciliated respiratory epithelium often with admixed mucocytes.[14] This proliferation is considered to be a response to a specific stimulus such as a local and chronic inflammation. Still, the proliferation itself is a normal response to another abnormal condition, in contrast to neoplasia, where the proliferation in itself is abnormal. Therefore, we suggest that REAH has a more hyperplastic than neoplastic appearance.

Our recent study showed a large recruitment of tryptase-producing mast cells in REAH. These mast cells were accumulated in the stroma and between epithelial cells of pseudoglands.[18] A constant expression of metalloproteinases MMP9 and a lesser degree of MMP2 expression were observed in epithelial cells in REAH. This investigation suggests that mast cells may play a central role of in the REAH formation.[18]

DIFFERENTIAL DIAGNOSIS

When the pathologist has experience with the histological aspect of REAH, the differential diagnosis is usually easier for the following lesions: inflammatory polyps, papillomas, hemangiomas, gliomas, dermoids, squamous cell carcinoma, olfactory neuroblastomas, lymphomas, and, particularly, inverted papillomas, which originate from the stratified squamous epithelium, and adenocarcinomas, which originate from the glandular epithelium.[16–18,29]

TREATMENT

In isolated form, complete surgical excision seems currently the treatment of choice, because this tumor has no tendency to regress spontaneously.[2,30] Endoscopic resection without aggressive surgery is sufficient. Cerebrospinal fluid leak is at risk because this lesion arises inside the olfactory clefts.[23] However, prior recognition before surgery can lead to a more careful removal of REAH from the olfactory clefts, allowing avoidance of this complication.

In NP-associated form, the surgery includes surgical procedures on both olfactory clefts and ethmoidal labyrinths. The procedure begins by a dissection of the ethmoidal labyrinth between the middle turbinate and the medial orbital wall. Consequently, the middle turbinate can be easily lateralized to operate within the olfactory cleft. The main concern is olfactory disturbances after surgery on the olfactory clefts. Our study shows that surgery on the olfactory clefts and ethmoidal labyrinths for NP associated with REAH can improve the olfactory function, which was measured using the Sniffin' Stick tests, at 6 weeks postoperatively.[24] However, postoperative olfactory recovery may depend on the status of the olfactory clefts on the CT scan.[37] Likewise, no patients reported worsening of his/her sense of smell after the surgery.[24]

The recurrence of REAH after surgery has rarely been reported in the literature.[18,25] However, the longest follow-up after surgery is only up to 3.8 years in the literature (Table 1). Therefore, systematic evaluation after long-term follow-up needs to be performed to know the real rate of recurrence.

Jo *et al*.[28] found the presence of REAH in 6/29 pathological specimens of patients with nonintestinal low-grade sinonasal adenocarcinoma and suggested a relation of REAH to adenocarcinomas or even potentially to be a precursor lesion. However, no data within the literature pointed out that REAH can transform to a malignant lesion. Several authors suggested that REAH is the result of an inflammatory process in response to the presence of another local disease.[2,23,25]

CONCLUSION

REAH of the nose is not a rare disease. The diagnosis of REAH should be suspected in front of a cerebriform, fleshy, pinkish mass on endoscopic examination and an opacified widening of olfactory clefts without bone erosion on the CT scan. Endoscopic resection is the treatment of choice and can improve nasal obstruction as well as the sense of smell. Additional investigations will be essential to improve our knowledge about this entity.

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