Sinonasal respiratory epithelial adenomatoid hamartomas: Series of 51 cases and literature review

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ABSTRACT

Background: *Respiratory epithelial adenomatoid hamartomas (REAHs) are rare, benign glandular proliferations of the nasal cavity, paranasal sinuses, and nasopharynx. This study aimed to expand our understanding of this entity by presenting a series of REAHs combined with a review of the pertinent literature.*

Methods: *A retrospective review was performed on all patients with a diagnosis of REAH from 2002 to 2011. Data were collected with respect to age, gender, clinical presentation, imaging, histopathology, treatment, and outcome. Because olfactory cleft expansion by imaging evaluation has been reported to suggest REAH, maximum olfactory cleft (MOCs) widths were also measured.*

Results: *Fifty-one cases of REAH included 37 male (72.5%) and 14 female subjects (27.5%) with a mean age of 58.4 years. Headache, nasal obstruction, rhinorrhea, and hyposmia were the most common presenting symptoms. Although 35(68.6%) were associated with concurrent inflammatory pathology, 16 (31.4%) presented as isolated lesions of the nasal cavity. Enlargement of MOCs was evident on computed tomography, with mean MOCs of 8.64 and 9.4 mm, in the coronal/axial planes, respectively. There were no statistically significant differences between MOCs of isolated (7.96 mm) versus MOCs of associated (9.63 mm) lesions ($p = 0.25$). Forty-nine were treated with endoscopic resection without evidence of recurrence after a mean follow-up of 27.2 months.*

Conclusion: *REAHs are rare sinonasal lesions that may appear as localized, isolated masses or more diffuse when in conjunction with other inflammatory processes. Irrespective of clinical presentation, endoscopic removal appears to be curative. Differentiation from more aggressive lesions is paramount to avoid unnecessarily radical surgery for an otherwise benign process.*

(Am J Rhinol Allergy 27, 322–328, 2013; doi: 10.2500/ajra.2013.27.3905)

Respiratory epithelial adenomatoid hamartomas (REAHs) are rare, benign glandular proliferations of the sinonasal cavity and nasopharynx (NP), first described as a specific clinicopathological entity by Wenig and Heffner in 1995.[1] In that original characterization, >70% of REAHs exhibited isolated nasal cavity involvement, with the posterior septum being the most frequent site of origin.[1] A peak incidence between the third and eighth decades was reported, with a 7:1 male/female predilection.[1] Nasal obstruction, rhinorrhea, hyposmia, and epistaxis were the most common presenting symptoms.[1] Macroscopically, REAHs appeared as edematous, yellow–pink masses with a glistening surface similar to inflammatory polyps but were generally darker, with a more indurated, rubbery consistency.[1]

Since Wenig's seminal series, literature regarding this lesion has been primarily limited to case reports and histopathological analyses. Consequently, other facets of REAH, such as its pathogenesis, imaging findings, and clinical significance remain largely unknown. Recent series have also questioned some of the characteristics initially designated as being distinguishing features of this entity, with REAHs often detected in conjunction with inflammatory processes in addition to appearing as isolated lesions.[2,3] Bilaterality has also been reported, along with involvement of the paranasal sinuses and olfactory cleft (OC).[2,3] Furthermore, imaging evidence of OC expansion has been found to be associated with REAHs, implicating the OC as a potential site of origin rather than the nasal septum.[4]

Accurate recognition and differentiation of REAHs from more aggressive sinonasal processes (*i.e.*, Schneiderian papilloma and low-grade adenocarcinoma) is critical to avoid subjecting patients to unnecessary radical surgery for benign disease. In this retrospective review, we aim to present a series of REAHs and compare our findings with the reports in the literature. The demographics, clinical behavior, radiographic features, histopathology, differential diagnosis, and management of REAHs are discussed. Furthermore, the mean maximum OC (MOC) widths and total nasal (TN) widths were also calculated to determine if expansion of the OC is potentially indicative of REAH.

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Accepted for poster presentation to the American Rhinologic Society Combined Otolaryngological Spring Meeting, Orlando, Florida, April 12–13, 2013

The authors have no conflicts of interest to declare pertaining to this article

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MATERIALS AND METHODS

The records of 51 patients with a diagnosis of REAH were identified from a retrospective chart review between 2002 and 2011. The study was approved by The Institutional Review Board of the Southern California Permanente Medical Group. The requirement for informed consent was waived. Data collected included age, gender, clinical presentation, laterality, site of involvement, imaging studies, operative findings, treatment, and evidence of recurrence. All pathology material was reviewed for the characteristic histological features as well as any concurrent pathology. Computed tomography (CT) images were analyzed for the presence of OC enlargement. Specifically, MOC and TN widths were measured on digital CT scans both in the coronal and in the axial planes using the protocol outlined by Lima *et al.*[4] The OC is bound superiorly by the cribriform plate, laterally by the middle turbinate, and medially by the nasal septum, as previously defined.[5] Lima *et al.* determined MOC and TN widths by measuring the maximum distance between the middle turbinate and medial orbital walls, respectively (Fig. 1).[4] The ratios of MOC to TN widths were also calculated for each patient. Statistical analysis was performed by a biostatistician using SAS Version 9.2 (SAS, Inc., Cary, NC) *t*-test to compare the mean difference between associated versus isolated REAHs. Two-tailed α-level was set at a value of $p < 0.05$ with a confidence interval of 95%.

RESULTS

Fifty-one patients with a histopathology diagnosis of REAH were identified between 2002 and 2011. Patient demographic data are summarized in Table 1. The majority of patients were men ($n = 37$; 72.5%) with 14 (27.5%) women, having an overall mean age of 58.4 years (men, 58.5 years; women, 58.1 years) and a range of 37–89 years.

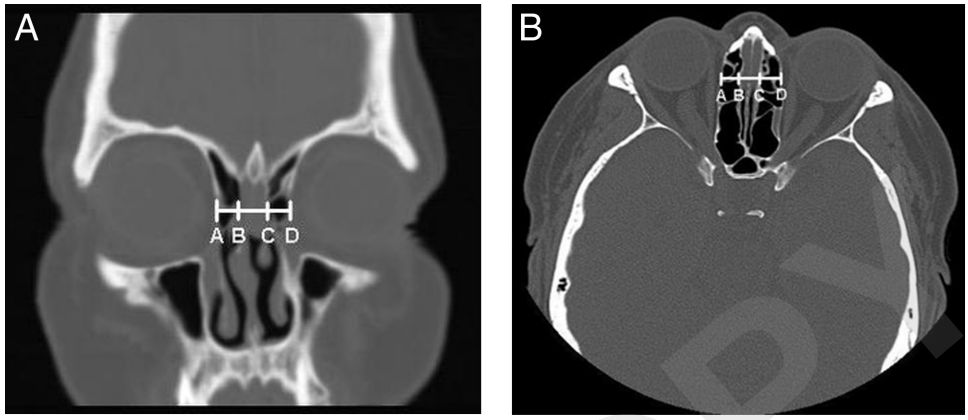

Figure 1. Preoperative (A) coronal and (B) axial computed tomography (CT) images illustrating methods of measurement for maximum olfactory cleft (MOC) and total nasal (TN) fossa widths as delineated by Lima et al.[4] *BC and AD distances correspond to MOC and TN widths, respectively. Note the bilateral opacification and characteristic widening of the OCs.*

Table 1 **Demographic data**

Feature	Result (n = 51)
Age	
Mean (yr)	58.4
Range (yr)	37–89
Gender	
Male	37 (72.5%)
Female	14 (27.5%)
Symptoms*	
Nasal obstruction	29 (56.9%)
Nasal congestion	19 (37.3%)
Hyposmia/anosmia	9 (17.6%)
Headache	9 (17.6%)
Rhinorrhea	7 (13.7%)
Facial pressure/pain	7 (13.7%)
Postnasal drip	4 (7.8%)
Epistaxis	2 (3.9%)
Ear plugging	1 (2%)
Location	
Paranasal sinuses	35 (68.6%)
Nasal cavity alone	16 (31.4%)
Laterality	
Unilateral	32 (62.8%)
Bilateral	19 (37.3%)
Recurrence	0

**More than one symptom may have been experienced by each patient.*

Table 2 **Isolated vs associated**

Feature	No.
Isolated	16
Bilateral	4
Unilateral	12
OC	9
Posterior nasal cavity/NP	7
Associated	35
Bilateral	15
Unilateral	20
SNP	20
CRS without polyps	12
Allergic fungal rhinosinusitis	3

CRS = chronic rhinosinusitis; OC = olfactory cleft; NP = nasopharynx; SNP = sinonasal polyposis.

Nasal airway obstruction (56.9%), nasal congestion (37.3%), hyposmia (17.6%), headache (17.6%), facial pain (13.7%), rhinorrhea (13.7%), and postnasal drip (7.8%) were the most common presenting symptoms. Two patients (3.9%) had a history of recurrent epistaxis, and one patient (2%) also complained of ear plugging. Clinically, 31.4% (16/51) presented as discrete, isolated lesions within the nasal cavity, and 68.6% (35/51) were associated with concurrent inflammatory disease. REAHs were detected bilaterally in 37.3% (19/51) of patients and unilaterally in 62.7% (32/51).

With respect to the isolated group, 56.2% (9/16) cases primarily involved the OC, while the remaining 43.8% (7/16) were localized to the posterior nasal cavity with extension into the NP. Associated REAHs appeared to be present diffusely throughout the paranasal sinuses. However, determining the precise sites of involvement was difficult because of the presence of concurrent pathology. Isolated REAHs were found to be unilateral in the majority of cases (75%, 12/16) with the remaining 25% (4/16) bilateral, a finding matched in the associated group: 57.1% (20/35) unilateral versus 42.9% (15/35) bilateral. In the associated group, sinonasal polyposis (SNP) was the most commonly described concurrent pathology, present in 57.1% (20/35) of patients. Chronic inflammation without SNP and allergic fungal rhinosinusitis was also observed, present in 34.3% (12/35) and 8.6% (3/35) of cases, respectively. No patients had synchronous sinonasal tract malignancy. Additional findings regarding isolated and associated REAHs are listed in Table 2.

On nasal endoscopy, REAHs appeared as polypoid masses that were darker tan and more indurated than sinonasal polyps (Fig. 2). In only three cases (5.9%) was the diagnosis of REAH made preoperatively. The remaining 48 cases (94.1%) were detected as incidental findings during pathology examination of the endoscopically removed specimens. By histology, the classic features of REAH were noted. There was a submucosal proliferation of small- to medium-sized, round to oval glands lined by pseudostratified ciliated columnar epithelium with admixed mucin-secreting (goblet) cells (Fig. 3). There was no pleomorphism or atypia. These glands were formed from invaginations of the surface respiratory epithelium, were widely spaced, and surrounded by thick, eosinophilic, hyalinized basement membrane material (Fig. 3). A vascularized fibrous stroma with scattered inflammatory cells was also present. In one case, islands of osseous metaplasia were seen, consistent with a subtype known as chondro-osseous REAH (COREAH; Fig. 4).

CT images were available for radiographic measurements in 39 of 51 patients. Collectively, expansion of the OCs was detected, with mean MOC widths of 8.6 and 9.4 mm in the coronal and axial planes, respectively. With respect to isolated lesions, the mean coronal and axial MOC widths, TN widths, and MOC/TN ratios were 7.8 and 8.0 mm, 24.9 and 23.6 mm, and 0.31/0.34, respectively. With respect to associated REAHs, coronal and axial MOC widths, TN widths, and

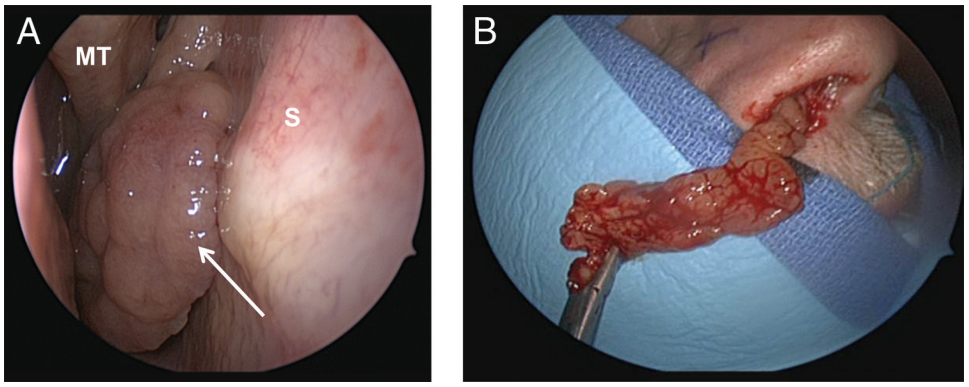

Figure 2. *On nasal endoscopy (A and B) REAHs appear as edematous, polypoid masses (arrow) with a glistening surface that are typically darker tan in color and more indurated than inflammatory polyps. S, septum; MT, middle turbinate; REAHs, respiratory epithelial adenomatoid hamartomas.*

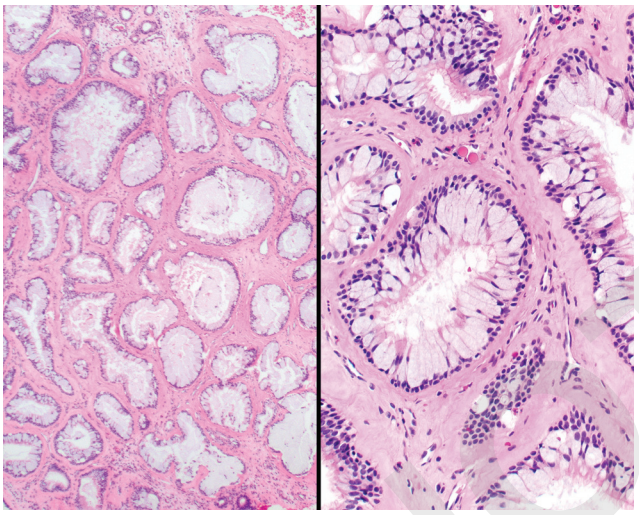

Figure 3. *The histological features of a REAH. (A) A low-power photomicrograph shows small to medium glands lined by respiratory epithelium admixed with numerous mucin-secreting goblet cells. (B) High-power photomicrograph shows a thickened basement membrane surrounding the glandular structures. Note the ciliated respiratory epithelium. REAH, respiratory epithelial adenomatoid hamartoma.*

MOC/TN ratios were 8.7 and 9.6 mm, 24.5 and 23.9 mm, and 0.32/0.40, respectively. Comparative analysis of isolated versus associated REAH MOC widths ($p = 0.45$ and $p = 0.25$), TN widths ($p = 0.71$ and $p = 0.83$), and MOC/TN ratios ($p = 0.37$ and $p = 0.40$) showed no statistically significant differences between the two groups in either the coronal or the axial planes. Mean MOC, TN, and MOC/TN measurements for isolated and associated REAHs are summarized in Table 3.

Forty-nine of 51 patients underwent successful endoscopic removal of the lesion. Isolated REAHs were managed with surgical excision, which involved dissection of the OC in nine cases and resection of the nasopharyngeal mass with posterior septal pedicle in seven cases. Associated REAHs underwent functional endoscopic sinus surgery (FESS) to treat concomitant sinus disease. No patients developed cerebrospinal fluid leak or any other complications postoperatively, and there has been no evidence of recurrent or persistent disease after a mean follow-up of 27.2 months (range, 6–65 months). Two patients, in which the diagnosis of REAH was made by biopsy in the clinic, declined to proceed with definitive surgery and were followed with serial endoscopies. There has been no growth in the lesions thus far after 6 and 7 months, respectively.

DISCUSSION

REAHs were first described as distinct clinicopathological entities by Wenig and Heffner in 1995.[1] They reported 31 cases involving the sinonasal cavity and NP collected from the files of the Otolaryngic Tumor Registry of the Armed Forces Institute of Pathology, the largest series to 2011. Demographically, the median age was 58 years (range, 27–81 years) with a strong male/female predilection (27:4). The primary presenting symptoms were nasal obstruction, nasal stuffiness, chronic recurrent rhinosinusitis, and epistaxis. The majority of cases (71%) were identified in the nasal cavity; the posterior septum was the most commonly affected site. Nasopharyngeal (3/31), ethmoid sinus (2/31), and frontal sinus (1/31) involvement were much less frequent. No concurrent pathology was identified except for one case each of Schneiderian papilloma, inverted type and a solitary fibrous tumor. These concomitant findings were interpreted by the authors to be coincidental rather than truly correlated with REAH. All patients underwent surgical excision and had no evidence of recurrence after 4 months to 5 years of follow-up.[1]

Since Wenig's seminal report, additional clinical information about REAHs has been limited to sporadic case reports and histopathological findings.[6,7] The largest study of REAHs published, to date, is by Vira *et al.* who presented a cohort of 54 patients treated with endoscopic resection between January 2000 and May 2011 (Table 4).[2] No pathognomonic symptoms, distinguishing endoscopic features, or radiographic traits were identified to suggest REAH. All cases were incidental findings discovered during routine pathological processing of sinonasal specimens acquired during FESS. All had associated findings, including 44 (81%) with chronic rhinosinusitis (CRS), 9 (17%) with SNP, and 1 (2%) with allergic fungal sinusitis. In contrast to Wenig's series, REAHs were observed more frequently affecting the sinuses (46/54; 85%) rather than appearing as isolated lesions of the nasal cavity (8/54; 15%). In terms of the latter, 25% (2/8) originated from the nasal septum, 37.5% (3/8) from the middle turbinate, and 37.5% (3/8) from the inferior turbinate. Involvement of the OCs was not reported and they were not separated into unilateral versus bilateral lesions. A recurrence or persistence rate of 3.7% (2/54) was reported after endoscopic removal with a mean follow-up of 3.8 years.[2]

Most recently, Hawley *et al.* reported on a series of 45 patients with REAHs collected between 2006 and 2011 (Table 4).[3] Lesions were separated according to clinical presentation, with 27% (12/45) presenting as "isolated" sinonasal masses and the remaining 73% (33/45) "associated" with another pathological process. In terms of isolated REAHs, the OC (9/12; 75%) was the primary site of origin followed by the middle turbinate (3/12), nasal septum (2/12), and sphenoid face (1/12). Furthermore, bilateral REAHs (8/12) were observed more frequently than unilateral lesions. With respect to associated REAHs, SNP was the most common concomitant finding (26/33; 79%) followed by malignancy (3/33), inverted Schneiderian papilloma (ISP; 2/33), adenoiditis (1/33), and hereditary hemorrhagic telangiectasia

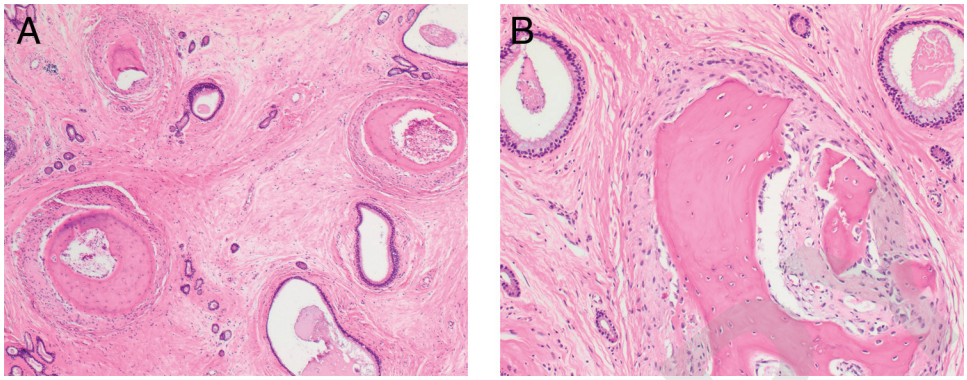

Figure 4. (A) A chondro-osseous REAH (COREAH) shows islands of bone (or cartilage) within the background stroma. Note the dilated glands with respiratory epithelium. (B) A high-power photomicrograph of a COREAH, showing the bone tissue within the stroma surrounded by the glandular epithelial units.

Table 3 **Radiographic data**

Feature	Total	Isolated	Associated	Isolated vs Associated
MOC width (mean, in mm)				
Coronal	8.64	7.81	8.74	$p = 0.45$
Axial	9.40	7.96	9.63	$p = 0.25$
TN width (mean, in mm)				
Coronal	24.55	24.85	24.45	$p = 0.71$
Axial	23.84	23.63	23.90	$p = 0.83$
MOC width/TN width (mean)				
Coronal	0.35	0.31	0.36	$p = 0.37$
Axial	0.38	0.34	0.39	$p = 0.40$

MOC = maximum olfactory cleft; TN = total nasal.

(1/33). Both isolated and associated REAHs were treated with endoscopic excision and no recurrence was detected after a mean follow-up of 9 (isolated) and 11 (associated) months, respectively.[3]

When analyzing the clinical aspects of this cohort in combination with the literature, several themes emerge (Table 5). Like Wenig's initial study, the overall mean age is 58 years with a male predilection of 2:1. Headache, nasal airway obstruction, nasal congestion, rhinorrhea, and hyposmia were the most common presenting symptoms. A majority (68.6%) of the cases were associated with SNP and/or chronic inflammation, with diffuse involvement of the paranasal sinuses. The remaining 31.4% presented as isolated lesions of the nasal cavity in which the OC was the most frequent site of origin (56.2%), followed by the posterior septum and NP (43.8%). REAHs are detected bilaterally in 53.1% (51/96) of patients and unilaterally in 46.8% (45/96), suggesting that bilateral involvement is much more common than initially described. Finally, irrespective of whether REAHs presented as isolated or associated lesions, endoscopic resection appeared to be curative similar to the outcomes of previous studies in the literature.

Histologically, REAHs are characterized by glandular proliferations of respiratory (pseudostratified ciliated columnar) epithelium that invaginate into the submucosa frequently maintaining continuity with the surface mucosa.[1] Classified as hamartomas, REAHs show excessive, disorganized, but self-limited overgrowth of this endogenous glandular component.[1] Glands appear as dilated, cyst-like structures with a lumen containing amorphous, mucinous material.[1] The glands are typically round to oval, small to medium, and separated by intervening stromal tissue. There is, overall, a polypoid appearance.[1,7] Periglandular hyalinization or collagenized stroma is prominent, associated with a mixed inflammatory infiltrate in the adjacent stroma.[1] Nuclear atypia is absent and mitoses are seldom identified.[1,7] In rare instances, osseous metaplasia or islands of cartilage may be interspersed within the lesion, a subtype known as COREAH.[8,9] Only one patient in this series presented with COREAH (Fig. 4). This lesion was managed with endoscopic resection, without recurrence at 6 months.

REAHs' hallmark histological features must be distinguished from two more aggressive disease processes in the differential diagnosis: ISP and low-grade, well-differentiated sinonasal adenocarcinomas (SNACs). ISPs arise from the surface Schneiderian epithelium and invaginate into the underlying stroma similar to REAHs. However, the cellular proliferation is a transitional squamoid epithelium in contrast to the adenomatoid respiratory epithelial-lined structures typically observed in REAHs.[1] Furthermore, ISPs have intraepithelial mucus cysts and an inflammatory infiltrate within the epithelium and intraepithelial cysts. SNACs may originate from either seromucinous glands or the surface respiratory epithelium.[1] The glands have a characteristic back-to-back cribriform growth pattern with no intervening stroma.[1] In addition, pleomorphism, mitotic figures, and nuclear atypia are often present.[1] Misinterpretation of REAHs as either ISPs or SNACs may lead to unnecessary radical surgery for an otherwise benign process. Ozolek *et al.* reported the immunohistochemical findings for REAH, which were positive for CK7, p63, and 34βE12 and negative for CK20, CDX-2, smooth muscle actin, calponin, and S100 protein.[10] Currently, immunohistochemistry does not play a major role in diagnosis of REAHs, but distinctive staining with lesions in the differential diagnosis may be of value.[10,11]

Radiographically, opacification of the affected sinuses with attachment to the septum was originally reported to be the most frequent CT finding for REAHs, particularly for unilateral disease.[6,12–14] In Vira's study, no distinguishing radiographic features were identified apart from results typically seen with CRS.[2] In rare cases in which the maxillary sinus is affected, periapical lucency on dental radiographs has also been described.[15] In bilateral lesions, widening of the OCs has been recognized as a unique imaging feature, which has helped differentiate REAHs from SNP.[4,16] Lima *et al.* compared the MOCs on CT in patients with REAHs, SNP, and no disease.[4] A statistically significant increase was evident in REAH patients, who possessed a median MOC width of 12.1/12.2 mm (in the coronal/axial planes) versus 5.4/5.6 and 4.2/4.5 mm for the SNP and control groups, respectively. The ratio of MOC/TN was determined with REAH patients showing the largest percentage: 44.7% versus 22.9% (SNP) and 19.1% (control). Concomitant lateralization of the middle turbinates and narrowing of the ethmoid labyrinth were also appreciated.[4] In Hawley's series, such olfactory fossae expansion was observed whether REAHs presented as isolated lesions or in association with other inflammatory processes.[3]

In the current cohort, the mean MOC was 8.64/9.40 mm in the coronal/axial planes with a MOC/TN of 35–38%. As expected, these values are greater than the MOCs and MOC/TN ratios Lima *et al.* had reported for the SNP and control groups in his series.[4] However, they are lower than the MOCs and MOC/TNs Lima *et al.* described for their REAH group.[4] This discrepancy is likely caused by differences in anatomic location between the two studies. Only patients with

Table 4 **Literature summary of REAHs**

Author	No. of Cases	Mean Age (yrs)	Sex	Location	U vs B	Isolated vs Associated	Treatment	F/U (yr)
Wenig and Heffner[1]	31	58 (27–81)	27 M 4 F	22, NC 1, ES 1, FS 3, NP	n/r	n/r 1, IP 1, SFT	Surgery	NED (0.3–5)
Lima *et al*.[4]	15	57 (38–93)	8 M 7 F	15, OC	B	5, I 10, A (8, SNP)	10, ESS 4, OC 1, Bx	NED (n/r)
Roffman *et al*.[9]	3	65 (56–80)	1 M 2 F	1, NC 1, MT 1, OC	B	3, A (2, SNP; 1, CRS)	2, ESS 1, Bx	NED (0.3–1)
Jo *et al*.[20]	6	62 (43–83)	5 M 1 F	4, NC 1, ES 1, S	U	6, A (low-grade SNAC)	6, Surg 3, XRT	NED (2.7)
Cao *et al*.[16]	3	49 (46–51)	2 M 1 F	3, OC	B	3, A (3, SNP; 1, AFS)	ESS	n/r
Vira *et al*.[2]	54	52 (n/r)	31 M 23 F	46, Sinuses 8, NC	n/r	9, SNP 28, CRS 24, Allergic sinusitis	ESS	2 with RD (3.8)
Hawley *et al*.[3]	45	55.9 (23–83)	26 M 19 F	33, Diffuse 9, OC 1, MT 1, SS 1, S	B, 8 U, 4	12, I 33, A (26, SNP; 2IP; 1, SCC; 1, ACC; 1,SNAC	12, ER 33, ESS	NED (0.75 and 0.9)
Aviles-Jurado *et al*.[21]	6	63.1 (35–80)	5 M 1 F	3, NC 1, ES 1, FS 1, MS	B, 3 U, 3	n/r	ESS	NED (2.3)

U = unilateral; B = bilateral; F/U = follow-up; M = male; F = female; NC = nasal cavity; ES = ethmoid sinus; FS = frontal sinus; NP = nasopharynx; OC = olfactory cleft; MT = middle turbinate; SS = sphenoid sinus; MS = maxillary sinus; S = septum; n/r = not reported; IP = inverted papilloma; SFT = solitary fibrous tumor; SNP = sinonasal polyposis; SNAC = sinonasal adenocarcinoma; AFS = allergic fungal rhinosinusitis; CRS = chronic rhinosinusitis; SCC = squamous cell carcinoma; ACC = adenoid cystic carcinoma, ESS = endoscopic sinus surgery; XRT = radiation therapy; ER = endoscopic resection; NED = no evidence of disease; RD = recurrent disease; I = isolated; A = associated; Bx = biopsy.

isolated REAHs occupying the bilateral OCs were included in Lima's series, whereas our study also encompassed patients with associated and isolated REAHs that primarily involved the posterior septum.[4] Otherwise, no statistically significant differences in MOC widths, TN widths, and MOC/TN ratios were found between isolated versus associated REAHs in our series.

Although REAHs were first thought to predominantly arise from the posterior septum, several reports describing REAHs affecting the OCs (REAH-OCs) have introduced the latter as a potential site of origin.[4,16,17] In Hawley's review, 75% of isolated REAHs occurred within the OCs.[3] Likewise, in this clinical series, the OC was involved in 56.2% of isolated lesions. Lima *et al.*, published the largest series of REAH-OCs, to date, in which all 15 cases discussed were localized to the anterior portion of the OC.[4] Lorentz *et al.* recently updated Lima's cohort to report their institution's cumulative 5-year experience with REAH-OCs.[18] Clinically, REAH-OCs either presented as bilateral lesions confined to the olfactory groove or in association with SNP within the ethmoid labyrinth (REAH-OC-NPs). In terms of the former, 12 isolated REAH-OCs were identified during the study period. With respect to the latter, the proportion of SNP cases in which REAH-OCs were concomitantly diagnosed increased over time as awareness of the lesion grew and the authors modified their surgical approach to enhance recognition of this disease. The detection rate for REAH-OC-NPs improved from 12.5 to 27% when the authors commenced sending OC specimens separately from ethmoid lesions for pathological processing, suggesting that REAH-OC-NPs may often go unnoticed and are likely being underdiagnosed.[18] In Vira's, Hawley's, and this cohort, associated REAHs were typically discovered as incidental findings during histological analysis of FESS specimens.[2,3] The actual incidence of REAH-OC-NPs may have been even greater if OC lesions were segregated from ethmoid disease as Lorentz had described. Because REAHs are often found concurrently with SNP, their diagnosis can be overlooked in favor of the more common, latter entity if pathologists do not recognize a second disease process is present within the same specimen.

Even with several reported series, many aspects of REAH remain unknown and are the subject of ongoing investigation. The etiology of REAH has yet to be delineated but is speculated to either be congenital in origin or be secondary to underlying inflammation.[1] Its shared clinical presentation, histological features, and frequent synchronous presentation with SNP have certainly lent support to the latter hypothesis.[1] In Hawley's and Vira's series, 73 and 61% of lesions were associated with an inflammatory process, respectively, with SNP being the most common concurrent pathology.[2,3] Likewise, in this cohort, 62.7% of REAHs were found in conjunction with CRS with and without SNP.

Although considered benign, lacking metastases and recurrence, REAHs have been shown to be locally aggressive.[13,14] Potential for intracranial and orbital extension can occur if left untreated, particularly in the setting of frontal sinus involvement.[13] Recent molecular genetic studies have also challenged REAH's original classification as a hamartoma.[19] Ozolek *et al.* examined the tumor gene profile of REAH, reporting a fractional allelic loss of 31%, intermediate between CRS (2%) and SNAC (64%).[19] Such an unusually high loss of

Table 5 **Combined clinical data (Current cohort with Literature)**

Feature	Number of Cases (n = 214)
Age	
Mean (yr)	57.7
Range (yr)	23–93
Gender	
Male	142 (66.4)
Female	72 (33.6)
Symptoms*	
Nasal obstruction	69
Nasal congestion	19
Hyposmia/anosmia	31
Headache	31
Rhinorrhea	38
Facial pressure/pain	30
Postnasal drip	10
Epistaxis	11
Dysgeusia	7
Ear plugging	1
Location*	
Paranasal sinuses	121
Nasal cavity alone	86
OC	37
Nasopharynx	3
Laterality*	
Unilateral	45
Bilateral	51
Other findings*	
Isolated	33
Associated#	90
SNP	68
CRS without polyps	41
Allergic fungal rhinosinusitis	4
Treatment	
Endoscopic resection	210
Biopsy/observation	4
Outcome*	
No recurrence	205
Recurrence	2

Source: Refs. 1–4, 9, 16, 20, and 21.
**Data not reported in all cases.*
#Some cases associated with more than one condition.
CRS = chronic rhinosinusitis; OC = olfactory cleft; SNP = sinonasal polyposis; yr = years.

heterozygosity rate (chromosomes 9p and 18q) raises the possibility REAHs may represent a benign neoplasm instead of a developmental malformation as initially postulated.[19] Furthermore, REAHs have also been found to exist in conjunction with low-grade tubular SNAC, suggesting a potential association between the two.[20] In Hawley's cohort, REAH was identified in the tissue margins of malignant lesions in three patients: squamous cell carcinoma, low-grade intestinal SNAC, and adenoid cystic carcinoma, respectively.[3] Similarly, Jo *et al.* presented six cases of low-grade tubular SNAC in which REAH was also detected.[20] Consequently, it has been hypothesized that REAH may serve as the initial event within a hamartoma—adenoma–adenocarcinoma spectrum.[21] However, whether REAHs represent true precursors to malignancy is yet to be determined. None of the patients in our series showed concurrent malignancy.

Successful treatment of REAHs involves complete surgical resection, frequently accomplished using a transnasal endoscopic procedure.[1,16] In patients with disease confined to the OCs, surgery may be primarily directed toward that area without the need for FESS if there is normal aeration of the paranasal sinuses.[18] However, meticulous care must be taken when surgically dissecting REAH-OCs due to their close proximity to the cribriform plate, to avoid any inadvertent violation of the skull base with subsequent complications.[18] In exceptionally rare cases where intracranial extension is present, resection of the olfactory bulbs with skull base reconstruction or an open craniofacial approach may be necessary.[13,22] However, because of its self-limiting growth and uncommon local recurrence after total excision, REAHs generally carry a very favorable prognosis.[1,16] In this series, all patients managed by endoscopic resection have no evidence of recurrence after a mean follow-up of 27.2 months.

CONCLUSION

REAHs are rare, unique clinicopathological entities that should be included in the differential diagnosis of sinonasal masses. Clinically, they may appear as isolated lesions localized to the nasal cavity or occur more diffusely throughout the paranasal sinuses in conjunction with other inflammatory processes. Irrespective of clinical presentation, endoscopic removal appears to be curative. Judicious identification and differentiation from similar but more aggressive lesions is paramount to avoid unnecessarily radical surgery for otherwise benign pathology. Radiographic evidence of OC expansion should raise the index of suspicion for REAH, although histological verification is required for definitive diagnosis. Further investigation is still needed to determine the pathogenesis, clinical significance, and relationship of REAHs to underlying inflammation and malignancy.

ACKNOWLEDGMENTS

The authors acknowledge Wansu Chen, biostatistician, for performing all statistical analysis calculations.

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