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ORIGINAL RESEARCH

Not just another nasal polyp: Chondro-osseous respiratory epithelial adenomatoid hamartomas of the sinonasal tract

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Abstract

Objectives: Chondro-osseous respiratory epithelial adenomatoid hamartomas (COR-EAH) are extremely rare benign lesions in the sinonasal cavity. We aim to (a) report two cases of COREAH and (b) perform a literature review with a summary on previously published cases of COREAH till August 2019.

Methods: A literature review identified 16 cases, but only 12 cases from publications from 2005 to 2019 were included in analysis. In addition, we report two cases of COREAH from our tertiary academic medical center.

Results: COREAH is found in patients from 3 to 83 years old. It originates from various sites in the nasal cavity and sinuses but the most common location is the lateral nasal wall. Calcification on imaging is a common finding.

Conclusion: COREAH is an uncommon entity that is important to recognize and distinguish from other sinister nasal masses. It is a slow growing benign lesion which lacks aggressive features on imaging. Future studies are needed to evaluate the possibility of an underlying genetic predisposition.

Level of Evidence: 4.

KEYWORDS CO, REAH, nasal hamartoma, nasal lesion, nasal polyp, REAH

1 | INTRODUCTION

Hamartomas of the head and neck generally, as well as the sinonasal tract specifically, are very rare. Nonetheless, the World Health Organization recognized its significance as a distinct entity in the new classification of head and neck tumors in 2017.¹ Prior to 1990s, the majority of hamartomas reported were mesenchymal.² Wenig and Heffner³ first described respiratory epithelial adenomatoid hamartoma (REAH), a pure epithelial-type hamartoma, in 1995. Osseous metaplasia was seen in one case which the author

later described to be chondroosseous respiratory epithelial adenomatoid hamartoma (COREAH). In the past decade, our understanding of nasal hamartomas has improved with an increasing number of cases reported in literature. The majority of hamartomas of this region are now known to be purely epithelial,⁴ but there can also be mesenchymal hamartomas or mixed epithelial-mesenchymal hamartomas. REAH represents the most common epithelial hamartoma; and at the other end of the spectrum lies nasal mesenchymal hamartoma (NCMH). COREAH is a unique and rare entity that lies in this continuum with both epithelial and mesenchymal

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FIGURE 1 Nasoendoscopy. A, View of left anterior nasal space. Yellow arrow points to left COREAH lesion. B, Lesion extends posteriorly to choana. Yellow arrow points to left COREAH lesion. C, Lesion attached to posterior nasal septum. Yellow arrow points to left COREAH lesion. D, Lesion attached to posterior nasal septum. Green arrow points to attachment to posterior nasal septum (A) View of left anterior nasal space. Yellow arrow points to left COREAH lesion.

Laryngoscope



(B) Lesion extends posteriorly to choana. Yellow arrow points to left COREAH lesion.



(C) Lesion attached to posterior nasal septum. Yellow arrow points to left COREAH lesion.



(D) Lesion attached to posterior nasal septum. Green arrow points to attachment to posterior nasal septum.



components. Cases of COREAH could have been classified as a subset of REAH because of their histological similarities and the difficulty in distinguishing native septal bone from lesional bony structure in some cases. We present two additional case reports of COREAH along with a literature review of previously published cases.

2 | CASE 1

A 54-year-old Chinese woman presented with progressively worsening left nasal obstruction for several months associated with hyposmia and rhinorrhea. She had no history of epistaxis or sinusitis. Nasoendoscopy revealed a large mass in the left nasal cavity extending from the left (A) Coronal CT images (bone window). Yellow arrow points to the left COREAH lesion.



FIGURE 2 A,B, Coronal CT images (bone window). Yellow arrow points to the left COREAH lesion. C, Coronal CT images (soft tissue window contrasted). Yellow arrow points to left COREAH lesion. D, Axial CT images (bone window). Green arrow points to patent left spheno-ethmoidal recess





(C) Coronal CT images (soft tissue window contrasted). Yellow arrow points to left COREAH lesion.



(D) Axial CT images (bone window). Green arrow points to patent left spheno-ethmoidal recess.



olfactory cleft to the nasal floor, and posteriorly to the choana. The mass appeared to originate from the left sphenoethmoidal recess and is confined within the nasal cavity and nasopharynx (Figure 1).

Interestingly, she has a history of multiple previous soft tissue tumors that were surgically excised. She underwent hysterectomy in 2007 for uterine leiomyomata and adenomyosis. She also underwent routine esophagogastroscopy in 2017 and an incidental cardioesophageal junction polyp was excised which turned out to be a benign fundic gland polyp. In 2017, she also had a $2 \times 1 \times 0.5$ cm left flank lesion that was a benign fibroepithelial polyp and another left arm lesion which was reported as consistent with a mixed dermal tumor (chondroid syringoma).

Computed tomography (CT) scan of the paranasal sinuses showed a 2.5×0.9 cm polypoidal lesion with internal calcification that was closely



FIGURE 3 COREAH. Nasal mass lined by respiratory epithelium and composed of loose fibrous stroma, cancellous bone and chondroid matrix. Invaginated submucosal glands lined by respiratory epithelium are noted between bony trabeculae. (Hematoxylin and eosin stain, $4 \times$ magnification)

related to the left posterior ethmoid sinus, possibly arising from the floor/ medial wall. This was seen extending inferiorly, mildly widening the ipsilateral olfactory cleft at its posterior aspect and extending into the nasopharynx through the posterior choana. There was resultant opacification and mild expansion of the posterior ethmoid sinus but no bony erosion. The left spheno-ethmoidal recess remained patent (Figure 2).

Incisional biopsy of the mass in clinic showed mild chronic inflammation and was inconclusive.

The patient subsequently underwent left functional endoscopic sinus surgery and excision of tumor. Intraoperatively there was a pale nasal mass on the left side, originating from the mucosa of the posterior nasal septum and the anterior face of the sphenoid (Figure 1). The mass was excised completely en-bloc with the mucosal attachments to the posterior septum and sphenoid face completely removed.

Macroscopic examination showed a hard mass with smooth glistening surface measured $4.5 \times 2.3 \times 2$ cm. Microscopic examination showed a solid mass lined by respiratory epithelium with invaginated glands lined by ciliated columnar cells and goblet cells between osseous trabeculae. Focal chondroid metaplasia was also noted. Some thick-walled vessels were noted in the stroma. Rare eosinophils were seen in the lamina propria. There was no evidence of granuloma, dysplasia or malignancy (Figure 3).

The patient was last reviewed at 1 year postoperatively and her sense of smell has improved. Sinus cavities were clean with no signs of recurrence.

3 | CASE 2

A 57-year-old man presented with right nasal obstruction and blood stained mucopus for 6 months. Nasoendoscopy revealed a large

polypoidal mass that occupied the entire right nasal cavity, extending into the postnasal space.

A CT scan of the paranasal sinuses showed a large polypoidal mass with internal coarse calcifications, measuring up to 6.1 cm. It was centered in the right nasal cavity and extended into the posterior nasal space. There was resultant occlusion of the right maxillary sinus, frontal sinus and sphenoid sinus without obvious bony destruction seen (Figure 4).

An incisional biopsy in clinic showed inflammation including eosinophils with no evidence of malignancy.

The patient subsequently underwent right functional endoscopic sinus surgery and excision of tumor. Intraoperatively there was a large right nasal mass attached to the right superior turbinate that occupied the entire anterior nasal cavity with inspissated mucus seen within the adjacent paranasal sinuses. The tumor was removed en-bloc with its mucosal attachments and part of the superior turbinate completely removed. Macroscopic examination showed a hard polypoid mass measured 5 \times 3.5 \times 2 cm. A bonv cut surface with numerous tinv cvstic spaces between bony tissue was noted. Microscopic examination showed cystic glandular proliferation composed of widely spaced cystic glands lined by ciliated epithelium with focal oncocytic metaplasia. The glandular proliferation was seen arising in direct continuity with the surface epithelium, which invaginated into the lamina propria. The glandular component was admixed with trabecular bone. The surrounding stroma appeared markedly edematous. There was no evidence of epithelial dysplasia or malignancy (Figure 5).

The patient was last reviewed at 8 months postoperatively. Sinus cavities were clean with no signs of recurrence.

4 | METHODS

An extensive review of the PubMed, EMBASE and Google Scholar databases was carried out until August 2019. A manual search through references of relevant publications was also conducted. All published case reports of COREAH as well as unpublished poster and abstract presentations were included in this review. The search yielded 13 publications that reported 16 cases including 2 abstracts and 1 poster presentation. Of these, only 11 publications^{5,6} that reported 12 cases were included in our analysis after excluding an abstract with limited information on the cases and a publication written in Japanese. Data was collected on patient demographics, laterality, site of disease, clinical presentation, comorbidities, investigation, treatment and follow-up. For the case reports, consent was taken from both patients for publication. Approval was not required from Singhealth Central Institutional Review Board.

5 | RESULTS OF LITERATURE REVIEW

Twelve cases of COREAH were included in analysis (Table 1), consisting of 5 males and 7 females. The patients varied widely in age, from 3 to 83 years old, with the median age at 42 years. Five cases



(B) Coronal CT images (bone window). Yellow arrow points to right COREAH lesion.



(C) Axial CT images (bone window). Yellow points to right COREAH lesion.



had lesions from the right and 6 from the left, and 1 case had bilateral nasal lesions. The majority was located in the nasal cavity, whilst 1 case developed in the ethmoid sinus. Out of the 11 cases in the nasal cavity, 1 did not specify the site of origin but the rest were lateral nasal wall (n = 4), posterior nasal septum (n = 2), olfactory cleft (n = 2), and middle turbinate (n = 2). The most common clinical presentations were nasal obstruction and facial pressure or pain, with

other symptoms such as olfactory dysfunction and rhinorrhea being less common. The symptoms were chronic in nature, with variable duration ranging from several weeks up to 3 years. Other than the oldest patient in our review, aged 83 who had a history of hypertension and transient ischemic attack, none of the other patients had documented past medical conditions. All cases either had computed tomography or magnetic resonance imaging of the paranasal sinus,

FIGURE 4 A,B, Coronal CT images (bone window). Yellow arrow points to right COREAH lesion. C, Axial CT images (bone window). Yellow points to right COREAH lesion



FIGURE 5 COREAH. The polypoid nasal mass composed of mature bone and cystic glands lined by respiratory-type epithelium. These cystic glands were present in close proximity to the bony tissue. Cartilaginous tissue was not identified in the nasal mass. (Hematoxylin and eosin stain, $4 \times$ magnification)

prior to surgery. Seven of these scans (58.3%) were reported to have bony density/ossification/calcification of the lesions. None of the lesions displayed bony erosion or intracranial extension through the cribriform plate. The diagnosis was made on histopathology for all cases, with the size of tumor ranging from 1.5 to 7.2 cm. None of the cases reported malignant transformation. The treatment of choice for all cases was surgical excision and there was a single case with documented recurrence at 1 year post-op.

6 | DISCUSSION

COREAH can be found in patients ranging from 3 to 83 years old with no clear sex predilection. Obstructive symptoms or pressure effects are often encountered though most can be asymptomatic in the early course of disease. These lesions are found mostly in nasal cavity, most frequently seen at the lateral nasal wall but may also be encountered in sinus cavity as a solitary or polypoid lesion. It is a slow growing benign lesion which lacks aggressive features on imaging studies. Ossification is a common feature due to its osseous component. Traditionally, it is thought to be a type of non-neoplastic mass of disorganized tissue though the etiology is unknown. Even though the cellular elements are mature, the normal architecture of the surrounding tissue is not reproduced. Unlike neoplasm, the growth is self-limiting. The demarcation between a hamartoma and a benign neoplasm is variably interpreted.^{7,8}

REAH mostly occurs in adults from third to the ninth decade of life with male preponderance and peaks in the fifth/sixth decade^{9,10} with 1 case reported in a pediatric patient. NCMH mostly occur in infants and young children below the age of one,¹¹ which suggests a congenital etiology as a result of an inborn developmental error.

COREAH is unique in that it is part of this continuum of hamartomatous lesions. Our literature review demonstrates that it occurs in both the pediatric and adult population with an age range of 3-83 years old. As opposed to REAH which has a male preponderance (which was thought to have been accounted for by the close association with nasal polyposis and the increased prevalence in men¹⁰), COREAH does not seem to have a clear sex predilection. Among the types of nasal hamartomas, COREAH is the least understood. To the best of our knowledge, there are approximately 660 reported cases of REAH,¹⁰ 48 reported cases of NCMH¹¹ and 16 reported cases of COREAH.

Depending on the size and location of the lesion, the clinical manifestation and duration may vary. However, all reported cases have common presenting symptoms which include nasal obstruction, facial pressure/pain, headache, rhinorrhea, hyposmia or epistaxis. The identification of this benign lesion is important because it can be difficult to distinguish from other sinister tumors such as inverted papilloma and low-grade sinonasal adenocarcinoma. The location of the lesion may not serve as an accurate clinical distinction. REAH is classically described to be located at the posterior nasal septum and many appear to originate from the olfactory cleft^{9,10,12,13} whereas inverted papilloma from lateral nasal wall.¹³ However, COREAH originates from varving sites with 33.3% of reported cases originating from the lateral nasal wall. Calcification has been described as a useful diagnostic clue radiologically^{14,15} as 58.3% of the cases from our literature review demonstrated such findings. Unlike NCMH, it usually does not demonstrate aggressive behavior such as intracranial or intraorbital extension. Nonetheless, the initial diagnosis can be difficult or mistaken radiologically as it is still a diagnosis made primarily on histology assessment.

COREAH is described part of a spectrum of harmatomatous lesions and serves as the morphological link between REAH on one end to NCMH on the other end. Histologically, REAH is composed of glandular proliferation lined by pseudostratified ciliated epithelium; widely spaced round to oval glands separated by stromal tissue with invagination into submucosa at some areas. The glands are also characteristically surrounded by hyalinized stroma with a thick eosinophillic basement membrane. Glandular dilatation and globet cell metaplasia are often seen, and small seromucinous glands may be also be present. In addition to histologic features seen in REAH, COREAH has an organized admixture of cartilaginous and/or osseous trabeculae. Distinction from NCMH is made by the presence of more spindle cell stromal elements in addition to the same epithelial component. Findings specific for inverted papilloma are the presence of immature squamous metaplasia and the lack of prominent periglandular hyalinzation. A characteristic finding of seromucinous hamartoma is the submucosal epithelial proliferation of glands, and although haphazardly, retains the lobular architecture.^{4,13} COREAH does not show features of adenocarcinoma such as nuclear stratification, dysplasia and increased mitotic rate.¹⁶

Little is known about the exact pathogenesis of COREAH but hypotheses suggesting genetic and inflammatory origins have been extrapolated from studies on REAH and NCMH. REAH is commonly associated with chronic rhinosinusitis and found to occur at high

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	Follow-up	6 months No residual/ recurrence	1 year No recurrence	9 months No recurrence	۲ Z
	Size	4 cm	۲ Z	6.8 cm	4.0 × 2.4 × 1.1 cm
	Treatment	Surgical excision	Surgical excision	Piecemeal removal with surgical excision	Complete removal with surgical excision
	Radiology investigation of paranasal sinus	CT: Soft tissue mass with slight septal deviation and expansion of the nasal cavity. No bony destruction. MRI: High signal on T2 weighted	CT: Heterogeneous partially ossified with no bony destruction	MRI: Heterogenous expansile mass with bony and cystic components	CT: Soft tissue isotense mass with focal enhancement and calcification. Mild deviation of the nasal septum with no erosion of the bone
	Duration of symptoms	6 months	3 years	Several weeks	Few months
	Clinical presentation	Nasal obstruction	Nasal obstruction and occasional left-sided headaches	Right side facial pain, hyposmia, poor sense of taste	Nasal obstruction
	Comorbidity	Υ. Ζ	īž	ĨŽ	ĪŽ
	Site of disease	Right lateral nasal wall, the anterior root being attrached to the middle turbinate/agger nasi region. Extends from anterior nares to posterior choana and superiorly to the cribriform plate	Left posterior nasal septum, extended to the skull base superiorly and the lamina papyracea laterally	Right ethmoid sinus	Left lateral wall of the cavity, extending into the sphenopalatine foramen and the ethmoid air cells, and protruding into the nasopharynx posteriorly
	Gender	Aale	Aale	Female	Female
	Patient age	11	26	34	8
	Author, publication, date	Flavin et al, ⁵ 2005	Roffman et al, ⁶ 2006	Choi et al, ⁷ 2006	Fedda et al, ⁸ 2013
	No.	TI III	N	т	4

TABLE 1 Summary of COREAH cases

	Follow-up	Recurred 1 year after excision	6 months No recurrence	1 year No recurrence	N.A	A.N	ĪŽ	(Continues)
	Size	Not mentioned	7.2 cm	5.0 × 3.4 × 1.0 cm	2.7 × 1.5 × 1.2 cm	1.5 × 1.3 × 0.8 cm	6.5 × 2.8 × 1.5 cm	
	Treatment	Surgical excision	Complete removal via surgical excision	Complete removal via surgical excision	Surgical excision	Surgical excision	Complete removal via surgical excision	
	Radiology investigation of paranasal sinus	None stated	CT: Heterogenous expansive mass with no bony destruction	CT: Mixed density mass	None stated	CT: Soft tissue mass with bony density	CT: Soft tissue mass with calcification with no bony erosion.	
	Duration of symptoms	1.5 years	6 months	1 year	Several weeks	Several years	3 years	
	Clinical presentation	Nasal obstruction Wilms tumor	Nasal obstruction, rhinorrhea	Nasal obstruction	Nasal obstruction and epistaxis	Facial pressure and congestion, rhinorrhea	Nasal obstruction, rhinorrhea, anosmia	
	Comorbidity	A.N	īž	A.N	N.A	A.N	۲. Z	
	Site of disease	Bilateral superior turbinates and superior meatuses	Posterior part of left olfactory cleft. Extends from anterior nares to posterior choana and superiorly to cribriform plate	Stalk from left olfactory cleft and occupies the entire nasal cavity	Right middle turbinate	Left nasal cavity lateral wall	Right lateral wall just posterior to uncinate process. Compressed the inferior turbinate and abuts the nasal septum, extends into anterior ethmoid cells superiorly and protrudes into nasopharynx posteriorly	
	Gender	Female	Male	Female	Male	Male	Female	
d)	Patient age	~	т	64	31	60	94	
: 1 (Continue	Author, publication, date	Nomura et al, ¹² 2014	Gaoli et al,° 2015	Chatzopoulos et al, ¹⁰ 2017	Beattie et al, ¹³ 2017 (Poster)		ldris et al,° 2018	
TABLE	Š	Ś	v	7	ω	6	10	

YU ET AL.

383

Follow-up	6 months no recurrence	A.N
Size	4.8 × 5.2 cm	5×3 cm
Treatment	Surgical excision	Surgical excision
Radiology investigation of paranasal sinus	CT: Mass with highly dense calcified core and did not enhance with contrast MRI: Slightly heterogenous though predominantly T2 hyperintense and T1 hypointense mass. Gadolinium contrast demonstrated a heterogenous, cerebriform appearance	CT/MRI: Soft tissue mass with calcification. No bony erosion
Duration of symptoms	6 months	3 years
Clinical presentation	Headache, intermittent perioral parasthesia, epistaxis	Headache, nasal obstruction, mid-facial pain
Comorbidity	Hypertension, transient ischemic attack	A.N
Site of disease	Left posterior septum	Right middle turbinate and extends to posterior nasal
Gender	Female	Female
Patient age	83	66
Author, publication, date	Daniel et al, ¹⁴ 2019	Nikolopoulos et al, ¹⁵ 2019
No	11	12

TABLE 1 (Continued)

frequency in patients with nasal polyposis,¹² suggesting an inflammatory origin driven by tryptase-producing mast cells. However, Ozolek and Hunt¹⁷ found from molecular studies that REAH has an increased fractional allelic loss as compared to chronic sinusitis, and propose the possibility that REAH may be a benign neoplasm. NCMH on the other hand has been associated with pleuropulmonary blastoma in a small group of patients. A systematic review done by Mason et al in 2015¹¹ reported 22.9% diagnosed with pleuropulmonary blastoma prior to NCMH. Of these patients, 5 had other comorbidities including three with Sertoli-Lleydig cell ovarian tumors and one with jejunal polyp. This suggests a possible underlying genetic predisposition and Stewart et al demonstrated genetic proof of NCMH tumor association with DICER1 mutation.¹⁸ Our first case's interesting medical history of uterine leiomyomata, fundic polyp, skin fibroepithelial polyp and chondroid syringoma would lend support to possible genetic basis in the pathogenesis of COREAH with increased risk of other soft tissue tumors though its rarity in literature would mean that more molecular and genetic studies need to be undertaken before any formal associations can be made. Of note, none of the COREAH cases reported in literature complained of symptoms of pre-existing chronic sinusitis or showed evidence of nasal polyposis.

7 | CONCLUSION

COREAH is an uncommon entity that is important to recognize and distinguish from other more sinister nasal masses. Occurring in both the pediatric and adult population, it originates from various sites in the nasal cavity and sinuses, but the most common location appears to be the lateral nasal wall. It is a slow growing benign lesion with lack of aggressive features and calcification on imaging is a common finding. Though the etiology is unknown, future studies are needed to evaluate the possibility of an underlying genetic predisposition.

CONFLICT OF INTEREST

The authors have no conflicts of interests to disclose.

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