



## Respiratory epithelial adenomatoid hamartoma with inflammatory nasal polyposis

Emre Gunbey<sup>a</sup>, Esra Kavaz<sup>a</sup>, Bilge Can Meydan<sup>b</sup>, Hediye Pinar Gunbey<sup>c</sup>, Hulya Savas Mutlu<sup>b</sup>, Recep Unal<sup>a</sup>

<sup>a</sup> Department of Otorhinolaryngology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

<sup>b</sup> Department of Pathology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

<sup>c</sup> Department of Radiology, Faculty of Medicine Ondokuz Mayıs University, Samsun, Turkey

### ARTICLE INFO

### ABSTRACT

#### Article History

Received 02 / 01 / 2016

Accepted 10 / 05 / 2016

#### \* Correspondence to:

Emre Gunbey  
Department of Otorhinolaryngology,  
Faculty of Medicine,  
Ondokuz Mayıs University,  
Samsun, Turkey  
e-mail: emregunbeymd@hotmail.com

Respiratory Epithelial Adenomatoid Hamartoma (REAH) is a type of hamartoma characterized by prominent glandular proliferations lined with ciliated respiratory epithelium originating from the surface epithelium. REAH should be differentiated from inflammatory nasal polyp, inverted papilloma and adenocarcinoma to avoid from more aggressive surgery then is needed for the REAH and to avoid from unnecessary long-term follow-up with medical treatments. In this report, we present a case of REAH who was followed up with topical and systemic steroids for years with the misdiagnosis of inflammatory nasal polyposis and discuss the clinical, radiological and histopathological features of the disease at increasing importance in recent years.

#### Keywords:

Hamartoma  
Nasal polyp  
Olfactory cleft  
Paranasal computed tomography  
Respiratory epithelial adenomatoid

© 2016 OMU

### 1. Introduction

Hamartomas are abnormal mixture of tissues with a localized excessive overgrowth in the cells and tissues of an organ. Hamartomas often occur in lung, liver, kidney and intestinal tract (Liang et al., 2007). Respiratory epithelial adenomatoid hamartoma (REAH) is a subtype of hamartoma, first described in 1995 (Wenig and Heffner, 1995). Until the last few years, REAH of the nose and paranasal sinuses was

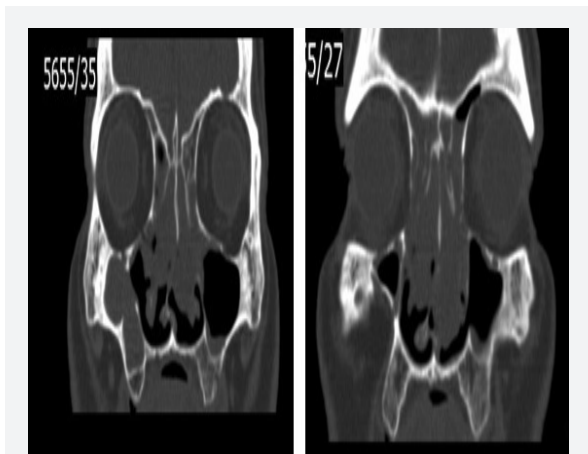
considered very rare and since Wenig and Heffner's cases in 1995 to last few years, about 10 REAH cases of nose have been reported (Himi et al., 2002; Metselaar et al., 2005; Ingram et al., 2006; Fitzhugh and Mirani, 2008; Cao et al., 2010; Braun et al., 2013). On the contrary, recent studies showed that REAH is much more common than expected and a significant proportion of patients with REAH were misdiagnosed and managed or treated with a diagnosis of inflammatory

nasal polyp, in the past (Gauchotte et al., 2013; Lee et al., 2013; Nguyen et al., 2014). In this article we present a case of REAH who was followed up with topical and systemic steroids for years with the misdiagnosis of inflammatory nasal polyposis and discuss the clinical, radiological and histopathological features of the disease of increasing importance in recent years.

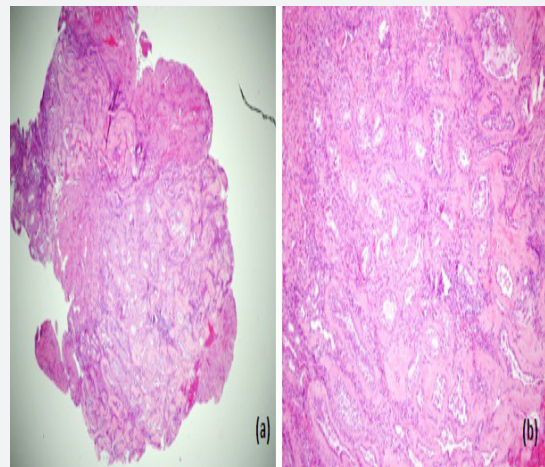
## 2. Case report

An 82-year-old male presented at our otolaryngology outpatient clinic with major complaints of nasal obstruction and hyposmia. He had a nasal operation history at another center for similar complaints ten years ago but there was no information about the content of previous operation and diagnosis. These complaints resumed after a short period postoperatively and the patient was long term managed by topical and systemic steroids with the diagnosis of inflammatory nasal polyposis. He denied any benefit from these treatments. His symptoms have worsened over a three-month period despite oral steroid and antibiotic medications. He had no history of systemic disease, allergy, malignancy, smoking or drug use. Endoscopic nasal examination revealed an anterior septal perforation about 3 mm in diameter and well-circumscribed, soft polypoid tissues that fills bilateral middle meatus and posterior nasal cavities. There was no mass lesion near the perforation and the perforation was thought to be due to the previous surgery or prolonged use of nasal steroids. Physical examination of the oral cavity, oropharynx, ears and neck was normal. An axial and coronal section computed tomography (CT) of the nose and paranasal sinuses was then performed to evaluate the extent of the disease. CT showed the presence of bilateral soft tissue densities at bilateral ethmoid and maxillary sinuses, olfactory clefts and

posterior nasal cavities and also a defect at the anterior nasal septum was detected. There was no destruction or invasion at the surrounding structures such as orbita, skull base or maxillary sinus walls (Fig. 1). The patient underwent an endoscopic sinus surgery. The polypoid tissues filling the bilateral middle meatus, olfactory cleft and nasal cavities were cleaned. The remnants of the middle turbinates was encountered secondary to previous surgery. Bilateral anterior and posterior ethmoidectomy and middle meatal antrostomy was performed and the pathologic tissues at the maxillary sinuses were removed. The operation was completed uneventfully. There were no complications during the postoperative period. Microscopic examination showed a large number of proliferated glands lined by ciliated respiratory epithelium and the surface of the lesion was found to comprise pseudostratified, ciliated columnar epithelium. There was no evidence of atypical cells or metaplasia (Fig. 2). The final histopathologic diagnosis was REAH. At 6-month follow-up, there was no evidence of recurrence.



**Fig. 1.** Paranasal sinus computed tomography showed the presence of bilateral soft tissue densities at bilateral ethmoid and maxillary sinuses, olfactory clefts and nasal cavities, also a defect at the anterior nasal septum was detected



**Fig. 2.** Microscopic examination showed a large number of proliferated glands lined by ciliated respiratory epithelium and the surface of the lesion was found to comprise pseudostratified, ciliated columnar epithelium (original magnification **a**:x40, **b**: x200, Hematoksylín&Eozín)

## 3. Discussion

Our traditional knowledge was requiring us to evaluate the bilateral bright gray or off-white color polypoid nasal masses as inflammatory nasal polyposis and to evaluate the topical or systemic steroids and endoscopic sinus surgery as treatment alternatives. In 1995, Wenig and Heffner have reviewed again the histopathological findings of patients who were operated because of nasal polyposis and described a type of hamartoma characterized by prominent glandular proliferations lined with ciliated respiratory epithelium originating

from the surface epithelium, called REAH, in 31 patients. The last few years, about ten cases of REAH were reported and REAH emphasized as a very rare clinical condition in the mentioned articles (Himi et al., 2002; Metselaar et al., 2005; Ingram et al., 2006; Fitzhugh and Mirani, 2008; Cao et al., 2010; Braun et al., 2013). However, an awareness occurred at this issue on recent years and many researchers reviewed histological findings of patients especially operated for inflammatory nasal polyps retrospectively and they realized that a significant portion of those patients the real diagnosis was REAH and actually they began to publish them. Lorentz et al. (2012), Vira et al. (2011), Lee et al. (2013) and Mühlmeier et al. (2014) published the largest series ranging from 25 to 50 cases. Studies revealed that REAH is a benign lesion predominantly affecting men after their third decades of life, with a mean age of 50-55 years. The most important complaints of REAH patients are nasal obstruction, loss of smell, headache and runny nose. REAH has been reported to cause more a loss of odor than nasal polyps. The most important reason is excess incidence of REAH at the olfactory cleft (Liang et al., 2007; Cao et al., 2010; Lee et al., 2013). Two form of REAH have been described as isolated and inflammatory with nasal polyposis. In published series approximately 70% of patients are reported to be with nasal polyps and 30% are isolated (Vira et al., 2011; Lorentz et al., 2012; Lee et al., 2013). Vira et al. (2011) found that 44% of cases of non-isolated REAH develop on allergic chronic sinusitis and 17% on nasal polyposis background. Isolated form is more seen in the olfactory cleft. The most distinguishing feature of our case was that both the olfactory cleft was affected and REAH was with extensive nasal polyposis. Lee et al. (2013) mentioned the affinity of REAH to the olfactory cleft and identified increased mean maximum olfactory cleft length in these cases. The studies on REAH found no etiologic role of Epstein Bar virus (EBV) and Human Papilloma virus (HPV) (Hua et al., 2014; Mühlmeier et al., 2014). The mechanisms driving the development of REAH are unknown, and its nature as a benign tumor, hamartoma, or reactive inflammatory process is still open to discussion.

Radiologically, the most common finding is an opacification of the affected sinus and connection to the posterior nasal septum. The majority of the cases reported to be bilateral. REAH must be suspected if there is opacification in CT and widening of the olfactory cleft (OC) (>10 mm), then REAH with inflammatory polyposis should be taken into consideration in the differential diagnosis to avoid overly aggressive skull-base surgery before biopsy confirmation of a benign lesion. Hawley et al. (2013) reported that when the olfactory cleft is 10 mm or more, the sensitivity and specificity for the presence of REAH are 88% and

74%, respectively CT reveals no more severe sinus disease in REAH with inflammatory polyposis, however, another important point is to evaluate that REAH can be accompanied by neoplastic lesions such as inverted papilloma, adenocarcinoma and hereditary hemorrhagic telangiectasia. Magnetic resonance imaging (MRI) of paranasal sinuses is rarely reported in REAH, reveals clearly delineated cerebriform tissue filling in the olfactory clefts. On MRI lesions are in hypo-iso intense signal characteristic compared to normal nasal septum in T1-weighted imaging and the enhancement pattern is variable T2-weighted images are observed as a hyperintense signal. In our case, there were widespread opacities in maxillary and ethmoid sinuses as well as an expansion at the olfactory cleft (Braun et al., 2013). We did not need preoperative MRI looking on CT to findings.

REAH appear as shiny polypoid masses, grey to white or yellowish in colour, with various sizes, on macroscopic evaluation. Microscopically, it is characterized with submucosal glandular proliferation with small to medium in size with prominent dilatation, which are lined with single layer of ciliated respiratory columnar epithelium. Cribriform structure and complex glandular growth is usually absent and the stroma contains inflammatory cells including eosinophils (Liang et al., 2007). Gauchotte et al. (2013) investigated the roles of tryptase producing mast cells and the production of metalloproteinases in REAH and concluded that the likely role of mast cell in REAH development may be metalloproteinase dependent. Our case bored the classic histopathologic features of REAH. A subtype of REAH was also defined, chondrosseous REAH that contains islands of cartilage interspersed throughout the lesion (Roffman et al., 2006). Although REAH is considered a non-neoplastic entity, molecular genetics findings suggest that REAH may in fact be a benign neoplasm.

REAH must be differentiated from other paranasal masses especially from an inflammatory polyp because of the clinical and histopathological similarities. The others in the differential diagnosis are inverted papilloma and adenocarcinoma. Clinically, inverted papillomas are more aggressive lesions, having the capacity to destroy bone and invade adjacent vital structures and histologically consisting of papillary fronds with a delicate fibrovascular core, covered by multiple layers of epithelial cells and characterized by invagination of the surface epithelium in the underlying stroma. Adenocarcinoma also shows invasion into the surrounding soft tissue and bone destruction, histologically originate from the glandular epithelium and are characterized by a complex glandular growth pattern with a back-to-back or cribriform pattern lacking intervening connective tissue (Vira et al., 2011; Lee et al., 2013). Immunohistochemically adenocarcinoma

demonstrates higher reactivity for mindbomb E3 ubiquitin protein ligase 1 (MIB-1) staining than REAH (Ozolek et al., 2007). Also, the lack of dysplasia, increased mitotic rate and cribriform architecture, and presence of individual glands surrounded by eosinophilic basement membranes, lined by ciliated respiratory epithelium in REAH, are criteria used to differentiate REAH from low grade adenocarcinoma

(Lee et al., 2013).

As a conclusion, the differential diagnosis is very important to avoid from more aggressive surgery than is needed for the REAH and to avoid from unnecessary long-term follow-up with medical treatments such as steroids. Because REAH is more resistant to topical and systemic steroids.

## REFERENCES

- Braun, J.J., Riehm, S., Averous, G., Billing, A., Veillon, F., 2013. MRI in respiratory epithelial adenomatoid hamartoma of nasal cavities. *J. Neuroradiol.* 40, 216-219. doi: 10.1016/j.neurad.2012.04.002.
- Cao, Z., Gu, Z., Yang, J., Jin, M., 2010. Respiratory epithelial adenomatoid hamartoma of bilateral olfactory clefts associated with nasal polyposis: Three cases report and literature review. *Auris Nasus Larynx.* 37, 352-356. doi: 10.1016/j.anl.2009.10.003.
- Fitzhugh, V.A., Mirani, N., 2008. Respiratory epithelial adenomatoid hamartoma: A review. *Head Neck Pathol.* 2, 203-220. doi: 10.1007/s12105-008-0064-3.
- Gauchotte, G., Marie, B., Gallet, P., Nguyen, D.T., Grandhaye, M., Jankowski, R., Vignaud, J.M., 2013. Respiratory epithelial adenomatoid hamartoma: A poorly recognized entity with mast cell recruitment and frequently associated with nasal polyposis. *Am. J. Surg. Pathol.* 37, 1678-1685. doi: 10.1097/PAS.0000000000000092.
- Hawley, K.A., Ahmed, M., Sindwani, R., 2013. CT findings of sinonasal respiratory epithelial adenomatoid hamartoma: A closer look at the olfactory clefts. *Am. J. Neuroradiol.* 34, 1086-1090.
- Himi, Y., Yoshizaki, T., Sato, K., Furukawa, M., 2002. Respiratory epithelial adenomatoid hamartoma of the maxillary sinus. *J. Laryngol. Otol.* 116, 317-318.
- Hua, X., Huang, X., Liao, Z., Xian, Q., Yu, L., 2014. Clinicopathological and EBV analysis of respiratory epithelial adenomatoid hamartoma. *Diagn. Pathol.* 25, 9:70. doi: 10.1186/1746-1596-9-70.
- Ingram, W.F., Noone, M.C., Gillespie, M.B., 2006. Respiratory epithelial adenomatoid hamartoma: A case report. *Ear Nose Throat. J.* 85, 190-192.
- Lee, J.T., Garg, R., Brunworth, J., Keschner, D.B., Thompson, L.D., 2013. Sinonasal respiratory epithelial adenomatoid hamartomas: Series of 51 cases and literature review. *Am. J. Rhinol. Allergy.* 27, 322-328. doi: 10.2500/ajra.2013.27.3905.
- Liang, J., O'Malley, B.W.Jr., Feldman, M., Newman, J.G., 2007. A case of respiratory epithelial adenomatoid hamartoma. *Am. J. Otolaryngol.* 28, 277-279.
- Lorentz, C., Marie, B., Vignaud, J.M., Jankowski, R., 2012. Respiratory epithelial adenomatoid hamartomas of the olfactory clefts. *Eur. Arch. Otorhinolaryngol.* 269, 847-852. doi: 10.1007/s00405-011-1713-9.
- Metselaar, R.M., Stel, H.V., van der Baan, S., 2005. Respiratory epithelial adenomatoid in the nasopharynx. *J. Laryngol. Otol.* 119, 476-478.
- Mühlmeier, G., Hausch, R., Arndt, A., Kraft, K., Danz, B., Maier, H., 2014. Respiratory epithelial adenomatoid hamartoma of the nose and nasal sinuses: A rare differential diagnosis of nasal polyposis. *HNO.* 62, 813-817. doi: 10.1007/s00106-014-2914-5.
- Nguyen, D.T., Nguyen-Thi, P.L., Gauchotte, G., Arous, F., Vignaud, J.M., Jankowski, R., 2014. Predictors of respiratory epithelial adenomatoid hamartomas of the olfactory clefts in patients with nasal polyposis. *Laryngoscope.* 124, 2461-2465. doi: 10.1002/lary.24778.
- Ozolek, J.A., Barnes, E.L., Hunt, J.L., 2007. Basal/myoepithelial cells in chronic sinusitis, respiratory epithelial adenomatoid hamartoma, inverted papilloma, and intestinal-type and nonintestinal-type sinonasal adenocarcinoma: An immunohistochemical study. *Arch. Pathol. Lab. Med.* 131, 530-537.
- Roffman, E., Baredes, S., Mirani, N., 2006. Respiratory epithelial adenomatoid hamartomas and chondroosseous respiratory epithelial hamartomas of the sinonasal tract: A case series and literature review. *Am. J. Rhinol.* 20, 586-590.
- Vira, D., Bhuta, S., Wang, M.B., 2011. Respiratory epithelial adenomatoid hamartomas. *Laryngoscope.* 121, 2706-2709.
- Wenig, B.M., Heffner, D.K., 1995. Respiratory epithelial adenomatoid hamartomas of the sinonasal tract and nasopharynx: A clinicopathologic study of 31 cases. *Ann. Otol. Rhinol. Laryngol.* 104, 639-645.