SINONASAL RESPIRATORY EPITHELIAL ADENOMATOID HAMARTOMA: A REPORT ON THREE CASES.

Carmelo Saraniti¹, Salvatore Gallina¹, Manuela Santangelo¹, Francesca Montana¹, Francesca Portelli², Elisabetta Orlando².

1. Department of Otolaryngology Head and Neck Surgery, University of Palermo, Azienda Ospedaliera Universitaria Policlinico Paolo Giaccone, Palermo, Italy.
2. Department of Pathology, University of Palermo, Azienda Ospedaliera Universitaria Policlinico Paolo Giaccone, Palermo, Italy.

ABSTRACT
Respiratory Epithelial Adenomatoid Hamartoma (REAH) is a rare benign lesion that may occur in the nasal cavity and paranasal sinuses. Histology is essential for the differential diagnosis with other lesions that could affect the sinonasal region. Our report focuses on three cases of male patients that were 46, 66 and 73 years old, diagnosed with REAH of the sinonasal region. All cases presented a nasal obstruction and hyposmia, and in one case cephalalgia. The definitive diagnosis of REAH was supported by the endoscopic, radiological and histological examinations. The patients underwent surgical excision with an endoscopic approach and did not experience a local recurrence at the time of writing this manuscript. REAH is a rare and often unrecognized clinical condition. The gold standard for treatment is complete surgical excision, which also allows for a correct histological diagnosis. Recurrence after surgery was not reported in our findings, as described in the literature.

1. Introduction
Respiratory epithelial adenomatoid hamartoma (REAH) is a rare benign lesion originating from the nasal cavity, paranasal sinuses, or nasopharynx.¹ In 1995, Wenig and Heffner were the first to describe this localization and coined the term REAH (Respiratory Epithelial Adenomatoid Hamartoma) referring to the histological features.² Since then, more than 394 cases of REAH have been reported in the literature, with a 3:2 male to female ratio.¹ Histologically it is characterized by adenomatous proliferation lined by respiratory ciliated epithelium, often with intermingled goblet cells.² The lesion can be clinically silent for a long time and the onset may be characterized by minor symptoms. Subsequently, due to a size increase, a unilateral or bilateral nasal respiratory obstruction, headache, craniofacial pain, rhinorrhea, epistaxis, proptosis and hyposmia may appear.³⁴ The diagnosis is based on an endoscopic examination and is supported by a typical CT finding of an inhomogeneous radiopacity contiguous to the olfactory cleft.⁵ A surgical excision of the lesion using an endoscopic approach results in a full recovery, and also allows to perform a histological examination of the surgical specimen for diagnostic confirmation. The histologic differential diagnosis of REAH includes inflammatory polyps, inverted Schneiderian papilloma and low-grade sinonasal adenocarcinoma, and less frequent tumors such as intranasal pleomorphic adenoma.

2. Cases presentation
Case 1
A 46-year-old male with a history of right-sided nasal obstruction and hyposmia; symptoms such as cephalalgia, rhinorrhea and other otorhinolaryngological symptoms were not present. Furthermore, the patient also reported a family history of neoplastic diseases (mother...
affected by meningioma with anosmia). The endoscopic examination only showed a swelling of the septal mucosa in Cottle’s area 4, near the olfactory cleft (Figure 1).

The diagnostic process was completed using a cone-beam CT-scan without contrast and Magnetic Resonance Imaging (MRI) with and without gadolinium.

The CT-scan showed a low-density lesion on the right side of the ethmoidal plate next to the olfactory cleft without evidence of bone erosion (Figure 2A).

The MRI provided clear structural details showing inhomogeneous intensity for the presence of low-density areolas in T1, and high-density areolas in T2 (Figure 2B-C).

Rare positive basal/myoepithelial cells for Ki-67 proved the low mitotic rate (Figure 4D).

The histology and immunohistochemical analysis, in addition to the clinical presentation and CT report, allowed us to diagnose REAH.

One month after surgery the patient presented total recovery of the olfactory function, and after one year there are no endoscopic and radiological signs of recurrence.

The surgical approach consisted in performing an en bloc endoscopic subperiosteal excision. The postoperative course was regular.

Macroscopically, the neoformation appeared red-brown in color, 2 cm in size. Histologically it was characterized by a proliferation of glandular spaces lined by ciliated respiratory epithelium (Figure 3).

Immunohistochemical analysis proved that the epithelial surface and stromal components were positive for CK7 (Figure 4A), and negative for CK20 (Figure 4B) and CDX2 (Figure 4C).

Case 2

The patient was 73-year-old male. One year after undergoing an ethmoidectomy for polyposis, the patient complained of a right nasal obstruction and hyposmia. The rhino-endoscopy showed a polypoid lesion that originated from the olfactory cleft and occupied the right nasal cavity. The CT scan without contrast confirmed the continuity of the mass with the olfactory region, which showed the typical flared cleft. There were no signs of bone erosion (Figure 5).
We proceeded with surgical excision of the lesion using an endoscopic approach. Macroscopically the neoformation appeared greyish in color with a multilobed surface, 3.5 cm in size, with a glistening and edematous appearance. Histologically it was characterized by a prominent glandular proliferation that included small and medium-sized glands, with a round and oval shape, covered with a thin layer of ciliated respiratory epithelium. The glands appeared frequently in direct continuity with the mucosal surface. A thickened and eosinophilic basement membrane surrounded them. The interposed stroma was edematous, fibrous, densely hyalinized or well vascularized and contained chronic inflammatory cells (Figure 6 A-B-C). The histology report was consistent with REAH. Also in this case, the follow-up after one year confirmed the effectiveness of the surgical procedure and the patient fully recovered his olfactory function.

Case 3
In this last case, REAH was diagnosed during an endoscopic surgery for nasal polyposis. The patient was a 66-year-old man.
Symptoms included bilateral nasal obstruction, headache and hyposmia. The nasal endoscopy showed the presence of bilateral polypoid lesions, translucent and not vascularized.
CT scans without contrast of the sinuses showed a hypodense tissue that occupied both nasal cavities, the ethmoid cells and the maxillary sinus presented no erosion of the bony walls (Figure 7).
The patient underwent ESS (Endoscopic sinus surgery) with complete removal of polyps.
Histological examination of the surgical specimens highlighted the simultaneous presence of inflammatory polyps and REAH. The sample had a polypoid appearance, with an irregular surface, 1.5 cm in size and histologically it was partially coated by ciliate respiratory epithelium, with dilated glands and chronic phlogistic infiltrate (Figure 8).
During the postoperative follow-up, the patient presented an improvement in nasal breathing and olfactory function. As in the first two cases, there are no signs of clinical and radiological recurrence after one year.

Figure 5 - CT scan without contrast confirmed the continuity of the mass with the olfactory region, which showed the typical flared cleft. There were no signs of bone erosion.

Figure 6 - The interposed stroma was edematous, fibrous, densely hyalinized or well vascularized and contained chronic inflammatory cells (Figure 6 A-B-C) (hematoxylin-eosin, original magnification 10x, 40x and 40x, respectively).

Figure 7 - CT scans without contrast of the sinuses showed a hypodense tissue that occupied both nasal cavities, the ethmoid cells and the maxillary sinus presented no erosion of the bony walls.
in a hyperplastic sinusitis in a milpolypoid appearance, yellowish or bloody discharge, an endoscopic examination is recommended. Huay et al. considered the pathognomonic characteristic of the olfactory cleft as typical radiologic finding, believing that it was crucial in the differential diagnosis. There were only seen in most intestinal adenomas and adenocarcinomas, whereas in the inflammatory diseases, specifically in REAH, the glandular proliferation tends to be submucous and does not have a cribriform architecture. The stromal component reveals hyalinization and focal areas of chronic phlogistic infiltrate.

In 2007, Ozolek et al. studied the histochemical profile examining an immunohistochemical panel, which was helpful for the differential diagnosis of REAH. The study showed that only basal cells were positive for p63 and 34βE12 in chronic sinusitis and REAH, whereas in the inverted papilloma there was a diffuse positivity for these markers. CK7 was expressed in both the inflammatory diseases, specifically in REAH, in inverted papilloma and adenocarcinoma. Finally, CK20 and CDX-2 were only seen in most intestinal-type sinonasal adenocarcinoma, and not in REAH or inverted papilloma. Also, in the first case we reported had the histochemical profile described.

In all cases, an asymmetry of the olfactory clefts diagnosis was suspected during the evaluation of the radiological data. We evaluated the coronal CT images using these parameters and we saw a significant enlargement of the olfactory cleft in all three cases we reported. MRI can show a hypointense lesion in T1 and hyperintense in T2 with peripheral contrast enhancement, which are non-specific for the diagnosis. Although the CT scan and MRI provide useful data, only the histopathological examination can exclude other sinonasal diseases, especially those characterized by severe progression (inverted papilloma and sinonasal adenocarcinoma), or those that may undergo malignant transformation, such as the rare case of intranasal pleomorphic adenoma.

Macroscopically, REAH shows a polypoid appearance, yellowish or pinkish with a variable size. The histological sections show a lobular adenomatoid proliferation with several tubular glands scattered on the ciliated columnar epithelium, as seen in a normal respiratory epithelium. The glandular proliferation tends to be submucous and does not have a cribriform architecture. The stromal component reveals hyalinization and focal areas of chronic phlogistic infiltrate.

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List of abbreviations

REAH: Respiratory epithelial adenomatoid hamartoma;
CT: Computed tomography;
MRI: Magnetic resonance imaging;
ESS: Endoscopic sinus surgery;
ENT: Ear, nose and throat;
REAH: REAH as isolated lesion;
TND: Total nasal distance;
OC: Olfactory cleft;

References


Figure 8 - Histological examination of the surgical specimens highlighted the simultaneous presence of inflammatory polypos and REAH. (hematoxylin-eosin, original magnification 4x)


