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Original article

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

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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.[3]

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.[2,4] 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

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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).

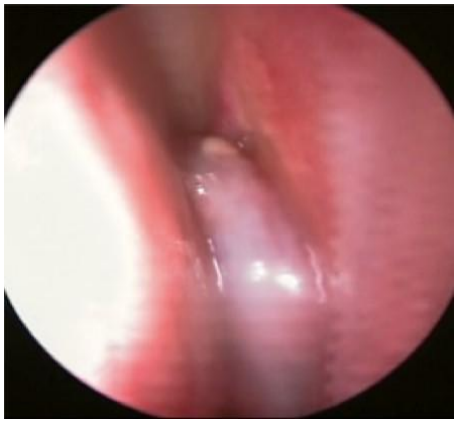

Figure 1 - Endoscopic examination.

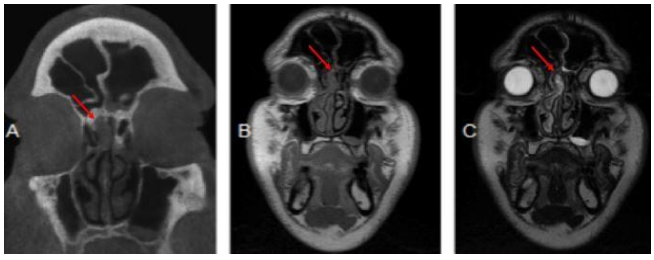

Figure 2 - CT-scan showed a low-density lesion on the right side of the ethmoidal plate next to the olfactory cleft without evidence of bone erosion (Figure 2A). MRI provided clear structural details showing inhomogeneous intensity for the presence of low-density areolas in T1, and high-density areolas in T2

The surgical approach consisted in performing an en bloc endoscopic sub-periosteal 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).

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.

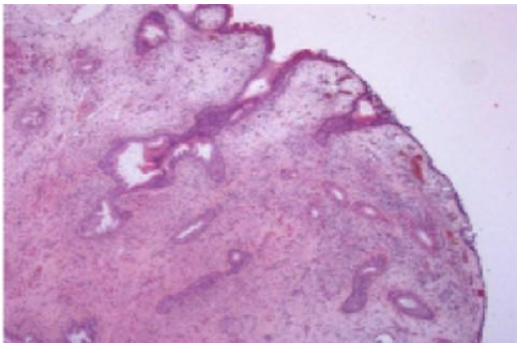

Figure 3 - Proliferation of glandular spaces lined by ciliated respiratory epithelium (hematoxylin-eosin, original magnification 4x).

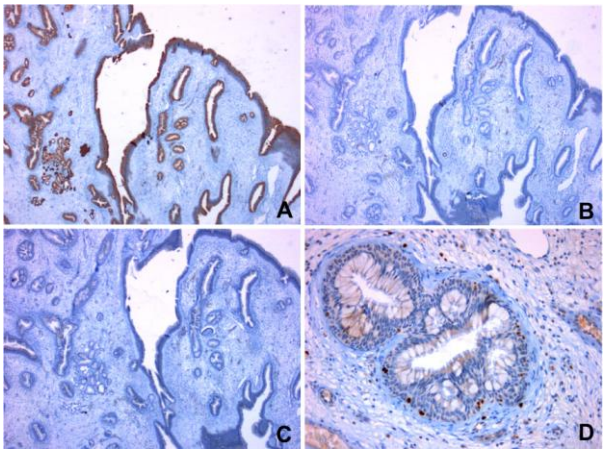

Figure 4 - The epithelial and stromal components are positive for CK7 (A, original magnification 10x), negative for CK20 (B, original magnification 10x) and CDX2 (C, original magnification 10x). Low mitotic rate evaluated with Ki-67 (D, original magnification 40x).

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.

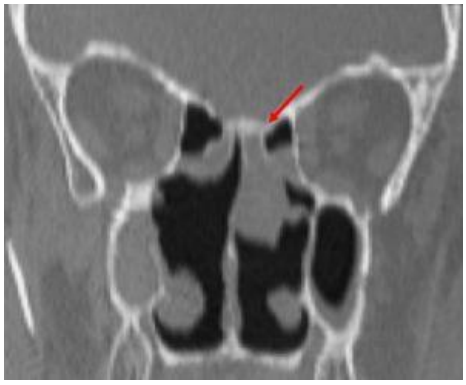

Figure 5 - CT scan without contrast confirmed the continuity of the mass with the olfactory region, which showed the typical flared cleft. There were no signs of bone erosion

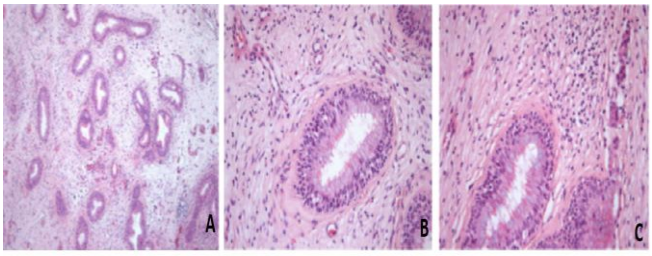

Figure 6 - The interposed stroma was edematous, fibrous, densely hyalinized or well vascularized and contained chronic inflammatory cells (Figure 6 A-B-C) (hematoxylin-eosin, original magnification 10x, 40x and 40x, respectively).

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.

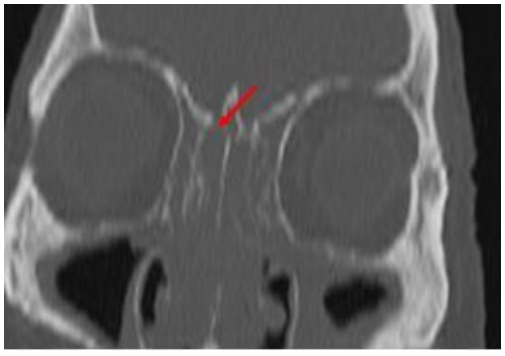

Figure 7 - CT scans without contrast of the sinuses showed a hypodense tissue that occupied both nasal cavities, the ethmoid cells and the maxillary sinus presented no erosion of the bony walls.

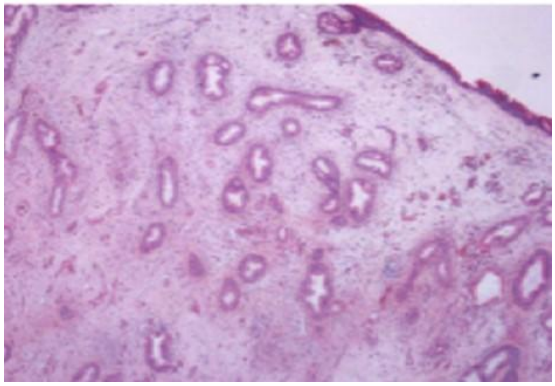

Figure 8 - Histological examination of the surgical specimens highlighted the simultaneous presence of inflammatory polyps and REAH. (hematoxylin-eosin, original magnification 4x)

3. Discussion

The etiology of the clinical condition discussed in this paper is still unknown, however, the importance of the inflammatory stimulus in the development of the lesion is recognized. The finding that there is a connection between REAH and chronic hyperplastic sinusitis in a statistically significant number of cases supports this hypothesis.[4,6]

Hyposmia is a typical symptom and may represent the only clinical manifestation in relation to the recent hypothesis that REAH originates in the olfactory area[5], as in the presented cases.

Subjective olfactometric evaluations were not considered to be necessary in all cases, as in the literature we consulted during our investigation.

The endoscopic exam usually reveals a unilateral polypoid lesion located in the olfactory region of the posterior nasal cavity, between the nasal septum and the middle turbinates.

In cases of REAH associated with nasal polyposis, the endoscopic diagnosis is more difficult because inflammatory polyps can also be observed in the olfactory clefts.

Lima et al. were the first to point out that REAH showed an enlargement of the olfactory cleft as typical radiologic finding, believing that it was crucial in the differential diagnosis.[5]

Hawley et al. considered the pathognomonic characteristic of the olfactory clefts with an enlargement > 10 mm associated with sinusitis. They performed a retrospective chart review to identify patients with a pathologic diagnosis of REAH. They identified 11 patients with REAH as an isolated lesion (REAHi), and 26 with REAH associated with nasal polyposis. The CT images of the two groups were compared with those of the 26 patients affected exclusively from polyposis (control group). The radiological parameters were the total nasal distance (TND), the olfactory cleft (OC) and the ratio of OC to TND. It was found that the OC and OC/TND were significantly larger in both groups of patients with REAH compared with control patients (P<0,01). No difference in TND was observed between these groups.[7]

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 exam can exclude other sinonasal diseases, especially those characterized by severe prognosis (inverted papilloma and sinonasal adenocarcinoma), or those that may undergo malignant transformation, such as the rare case of intranasal pleomorphic adenoma.[8]

Macroscopically, REAH shows a similpolypoid appearance, yellowish or pinkish with a variable size. The histological sections show a lobular adenomatoid proliferation with several tubular glands scattered on the ciliate columnar epithelium, as seen in a normal respiratory epithelium. The glandular proliferation tends to be submucosus and does not have a cribriform architecture. The stromal component reveals hyalinization and focal areas of chronic phlogistic infiltrate.[3]

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.[9] Also, in the first case we reported had the histochemical profile described.

REAH does not have the tendency to spontaneously regress, although it grows in a self-limiting mode. Thus, it is necessary to completely remove the lesion using the endoscopic approach. In the rare cases described in the literature with an intracranial and orbit invasion, an endoscopic approach associated with a frontal craniotomy was necessary. No recurrence after surgery is reported in the literature**.**

List of abbreviations

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

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