REVIEW ARTICLE

The Importance of the Differential Diagnosis in Rhinology: Respiratory Epithelial Adenomatoid Hamartoma of the Sinonasal Tract

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Abstract

Introduction: Respiratory epithelial adenomatoid hamartoma (REAH) is an uncommon lesion of the nasal and paranasal sinuses. It was first described in 1995 by Wenig and Heffner, and only about 60 cases have been published since then.

Material and methods: We present six case studies of nasal cavity hamartoma diagnosed and treated at our institution between 2005 and 2010. We also conducted a literature review and comprehensive study of the differential diagnosis of this condition, both clinical and pathological.

Results: The male–female ratio was 5:1, with a mean age of 63.1 years. The most frequent symptoms were nasal obstruction, rhinorrhea and loss of smell. All cases were treated with endoscopic sinus surgery, without recurrences in the follow-up period (28.2 months; SD=11.5 months).

Conclusion: We suggest that differential diagnosis should be made on the basis of nasal polyps, antrochoanal polyps, inverted papilloma and low-grade adenocarcinoma. This review of published cases is of equal interest to both pathologists and otorhinolaryngologists.

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Importancia del diagnóstico diferencial en rinología: hamartoma respiratorio adenoepitelial

Resumen

A Hamartoma respiratorio adenoepitelial (HRA) es una lesión poco común de la nariz y los senos paranasales caracterizada por la formación anormal de tejido glandular. Fue descrita por primera vez por Wenig y cols., en 1995 y, desde entonces, tan sólo se ha publicado unos 60 casos.

Material y métodos: En este trabajo, presentamos el estudio de seis casos de hamartoma de cavidad nasal, los cuales fueron diagnosticados y tratados en nuestro Centro entre los años 2005 y 2010. Asimismo, realizamos un estudio completo del diagnóstico diferencial de esta patología, tanto a nivel clínico como anatomopatológico.

Resultados: En estos pacientes, la razón hombre:mujer fue 5:1, con una media de edad de 63,1 años (DE=16,9). Todos los sujetos presentaron afectación de la fosa nasal y, en tres casos, ocupación de los senos maxilar, frontal y etmoidal. Los síntomas más frecuentes fueron obstrucción nasal, rinorrea y pérdida de olfato. Todos los casos fueron tratados mediante cirugía endoscópica nasal y/o sinusal sin evidencia de recurrencia en el periodo de seguimiento (28,2 meses, DE=11,5). Las características más importantes del HRA son: oedema estromal, proliferación glandular seromucosa, proliferación fibroblástica y vascular, infiltrado inflamatorio mixto, incremento de la proliferación adenomatoid, acúmulo de material glandular y cambios atróficos del epitelio. Conclusión: Sugerimos que el diagnóstico diferencial debe realizarse con la poliposis nasal y/o sinusal, pólipo antrocaanal, papiloma invertido y adenocarcinoma. Un diagnóstico incorrecto podría dar lugar a un tratamiento demasiado agresivo. Esta revisión de los casos publicados, con énfasis en el diagnóstico diferencial, es de interés tanto para otorrinolaringólogos como anatomopatólogos.

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Introduction

The term hamartoma (from the Ancient Greek hamartia, meaning error, and -oma, benign growth) was coined by Albrecht in 1904 to designate malformations consisting of an excessive but localised overgrowth in the cells and tissues of an organ. Hamartomas are common in the spleen, liver, lung, kidney and intestine, but are rarely found in the upper aerodigestive tract.1,2 In the work done by Wenig and Heffner,3 we can find the first definition of a specific type of hamartoma, known as adenoe-pithelial or respiratory epithelial adenomatoid hamartoma (REAH). It is characterised by abnormal glandular formations arising from the nasal cavity, paranasal sinuses and nasopharynx. This type of hamartoma is extremely rare: there have only been about 30 cases reported since the study by Wenig and Heffner in 1995.4-16

Due to its histological features, REAH can be mistaken for papilloma, nasal polyp, antrochoanal polyp (ACP) and even with low-grade adenocarcinoma. Consequently, the differential diagnosis is crucial in this entity.

This study presents six cases treated at the otolaryngology service between 2005 and 2010, together with a discussion of their differential diagnosis and a review of the published series.

Study Population

In these six cases, the male:female ratio was 5:1, with a mean age of 63.1 years (SD=16.92) (Table 1). All cases presented an occupation of the nasal cavity and three of them (50%) also showed an occupation of the maxillary (Fig. 1A), frontal and ethmoid (Fig. 1B) sinuses. Three patients (50%) presented unilateral involvement and symptoms. The most common symptoms were nasal obstruction and rhinorrhea (83.3%), while two patients (33.3%) suffered the loss of smell.

All tumours were treated by endoscopic sinonasal surgery (ESS) under general anaesthesia. The postoperative follow-up found no immediate surgical complications and patients were discharged within 24 h. The anatomopathological examination revealed changes that included oedema, inflammation and increased vascularity. Similarly, a submucosal adenomatoid proliferation was observed, which originated in the surface epithelium. This showed continuity with invaginations of similar appearance. All patients are currently alive and without evidence of disease or complications during the follow-up period (28.2 months, SD=11.5).

Discussion

Hamartoma is a rare tumour, characterised by an abnormal mixture of tissues unique to the region where they appear. The development of hamartomas may involve alterations in foetal growth or may result from immature tissue alterations during the postnatal period.4 They commonly appear in the lung, liver, spleen and kidney, and are rare in the head and neck region.
This type of tumour presents an unusual combination of tissues with an excess of one or more cellular components.\textsuperscript{5,6} Teratomas, dermoid tumours and hamartomas have an excessive growth of normal tissue layers, which often give rise to a tumour. In contrast to neoplasms, hamartomas are not capable of growing continuously and are, therefore, self-limited.\textsuperscript{3,5,17}

In addition, REAH are associated with surface epithelium, which invaginates into the submucosa while maintaining direct continuity with the mucosal surface. The main morphological feature of this lesion is the proliferation and accumulation of glands and ducts covered by pseudostratified ciliated epithelial cells with no atypical or metaplastic changes. These glands are surrounded by an eosinophilic base membrane and are implanted into the connective tissue, which goes from oedematous and/or inflammatory to thickly hyalinised.\textsuperscript{3,17} There have also been occasional reports of respiratory epithelium invaginations towards these glands\textsuperscript{5} (Fig. 1C and D).

Wenig and Heffner distinguished this lesion from common sinonasal polyps, while recognising the overlap in their clinical presentations, pathological changes, treatments and biological behaviours. The absence of recurrence or continued growth would exclude these lesions from the classification of neoplastic proliferation. Similarly, Endo et al.\textsuperscript{5} believe that REAH does not represent a neoplastic entity.

Approximately 70\% of REAH develop in the nasal cavity, usually in the posterior part of the nasal septum\textsuperscript{1,10}; other locations would include the nasopharynx, ethmoid, frontal and maxillary sinuses.\textsuperscript{3,4,7,10,12} After reviewing the literature (Table 2), over 90\% of cases (according to Athrea and Ducic\textsuperscript{5}) and 70\% (according to Roffman et al.\textsuperscript{10}) presented isolated involvement of the nasal cavity. According to the latter authors, the mean age would be 58 years, with a strong male preponderance (male:female ratio of 7:1). No aetiological agents such as tobacco or alcohol or other occupational or environmental factors were identified.\textsuperscript{3,6} In the largest study of REAH, Wenig and Heffner published 31 cases, 27 men and 4 women with a mean age of 58 years (27–81 years), reporting multiple symptoms, including nasal obstruction, rhinorrhea, epistaxis and chronic rhinosinusitis. In addition, Lima et al.\textsuperscript{11} presented the second largest series with 15 cases, 8 men and 7 women, with a mean age of 57 years (38–93 years). Chronic nasal symptoms, from 2 to 20 years, and the combination of nasal obstruction and anosmia/hyposmia were present in most cases. Athrea and Ducic\textsuperscript{5} reported that REAH could be accompanied by headache, proptosis and hyposmia. Furthermore, one case of maxillary sinus REAH was published, presenting it as a periapical radiolucency of the first molar, lacking in sinonasal symptoms.\textsuperscript{7}

Only one case of combined hamartoma and papilloma has been published\textsuperscript{9} and it was considered as a coincidence. Wenig et al. and subsequent studies do not consider REAH as a neoplastic lesion; however, no molecular evidence is available to accept or reject this assertion.\textsuperscript{18}

With respect to its origin, the aetiology of REAH remains unknown. Two main hypotheses are considered. One suggests that it is composed of hamartomatous proliferations and is probably congenital. An alternative theory, supported by the coincidence of both diseases (polypsis and REAH), suggests that REAH is associated with chronic rhinosinusitis
Figure 1  Radiological (CT) and anatomopathological image of respiratory epithelial adenomatoid hamartoma. (A) Unilateral opacity of the right maxillary and ethmoid sinuses. (B) Bilateral opacity between the middle turbinates and the nasal septum. (C) The respiratory epithelium is pseudostratified and ciliated (PCE) with presence of mucocytes (M) (haematoxylin–eosin, 40×). BM: basal membrane; GL: gland lumen. (D) Respiratory epithelial adenomatoid hamartoma in whose glandular proliferation there is continuity with the surface epithelium (arrows) (haematoxylin–eosin, 100×).

Table 2  Study of Cases Within the Medical Literature.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Symptoms</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wenig and Heffner, 19951</td>
<td>31</td>
<td>Nasal obstruction, epistaxis, rhinorrhea</td>
<td>Nasal fossa, ethmoid and frontal sinuses, nasopharynx</td>
</tr>
<tr>
<td>Himi et al., 20024</td>
<td>1</td>
<td>Nasal obstruction, rhinorrhea</td>
<td>Maxillary sinus</td>
</tr>
<tr>
<td>Endo et al., 20055</td>
<td>1</td>
<td>Obstruction, protrusion of hard palate</td>
<td>Nasal fossa</td>
</tr>
<tr>
<td>Delbrouck et al., 20066</td>
<td>1</td>
<td>Nasal obstruction, hyposmia, association with nasal polyps</td>
<td>Nasal fossa</td>
</tr>
<tr>
<td>Kessler and Unterman, 20047</td>
<td>1</td>
<td>Odontogenic presentation</td>
<td>Maxillary sinus</td>
</tr>
<tr>
<td>Athre and Ducic, 20058</td>
<td>1</td>
<td>Proptosis, headache</td>
<td>Frontal sinus</td>
</tr>
<tr>
<td>Ingram et al., 20069</td>
<td>1</td>
<td>Facial pain, nasal obstruction</td>
<td>Nasal fossa</td>
</tr>
<tr>
<td>Roffman et al., 200610</td>
<td>2</td>
<td>Polyposis, nasal obstruction</td>
<td>Pansinusosal, nasal fossa</td>
</tr>
<tr>
<td>Lima et al., 200611</td>
<td>15</td>
<td>Nasal obstruction, hyposmia</td>
<td>Nasal fossa</td>
</tr>
<tr>
<td>Liang et al., 200712</td>
<td>1</td>
<td>Nasal obstruction, epistaxis</td>
<td>Nasal fossa, ethmoid and maxillary sinuses</td>
</tr>
<tr>
<td>Caltabiano et al., 200813</td>
<td>1</td>
<td>Nasal obstruction</td>
<td>Nasal fossa</td>
</tr>
<tr>
<td>Gajda et al., 200914</td>
<td>1</td>
<td>Nasal obstruction</td>
<td>Nasal fossa</td>
</tr>
<tr>
<td>Cao et al., 201015</td>
<td>3</td>
<td>Nasal obstruction, hyposmia</td>
<td>Nasal fossa</td>
</tr>
<tr>
<td>Seol et al., 201016</td>
<td>1</td>
<td>Nasal obstruction</td>
<td>Nasal fossa</td>
</tr>
</tbody>
</table>
and a prolonged pro-inflammatory environment. Due to the fact that these lesions are relatively rare and few cases have been reported, there is little evidence as to their aetiology.18
In this series, the diagnosis of REAH associated to nasal polyposis supports the hypothesis that inflammation may induce the development of REAH.15

Knowledge and identification of these lesions is fundamental, as they can be microscopically mistaken with other, far more aggressive tumours, such as inverted papilloma or low grade adenocarcinoma. This in turn may lead to unnecessarily aggressive surgical resection. A wide range of surgical procedures has been used to treat this disease: maxillectomy, lateral rhinotomy, ethmoidectomy or transfacial approaches. Our view is that ESS can be used as a first-line treatment for these tumours in terms of efficacy, safety and absence of recurrence.

Differential Diagnosis

The main differential diagnosis of REAH is usually done with antrochoanal polyps (ACP) and nasal polyposis. Nevertheless, a complete differential study should be performed, including inverted papilloma and adenocarcinoma (Table 3). Although we did not find any mention of ACP as an entity to be considered in the differential diagnosis in the reviewed series, we believe that it should be considered as such, due to the similarity in clinical and macroscopic presentation.

The anatomopathological diagnosis of REAH can be very difficult, since distinguishing between benign and malignant glandular lesions of the sinonasal tract is not easy, especially in the case of small or fragmented biopsies.

While there are few immunohistochemical studies of REAH,5 it is increasingly common to find articles describing specific markers. Recently, Ozolek et al.18 presented CK7, p63 and HMWK. Regardless of their unknown pathophysiology, hamartomas are not capable of constant growth without obstacles and, therefore, their proliferation is self-limited.3,6,12 In contrast with the diseases described in the following sections, its excision is curative. No recurrences have been reported in the medical literature reviewed.3,5,7,12,19,20

Nasal Polyps

In contrast with REAH, nasal polyps rarely show septal involvement. Histologically, polyps present stromal oedema and a mixture of inflammatory cells similar to adenomatoid hamartomas. Adenomatoid proliferation and the absence of a seromucous gland component make it possible to differentiate between REAH and inflammatory polyps. The histological differences between inflammatory polyps and REAH would be the amount of adenomatoid proliferation, the material mimicking a basal membrane enveloping the glands and atrophic changes in the epithelium. Surgery is recommended in the case of sinonasal polyposis, when optimal medical treatment fails.21

The key feature for the differentiation of this inflammatory disease with respect to REAH is the presence of extensive glandular proliferation. REAH affects the nasal septum, especially in its posterior area. Furthermore, it presents a wider extension and is more indurated than nasal polyps. On the other hand, Lima et al.11 conducted an interesting radiological study by examining changes in CT scans of REAH and polyps, proposing various measures that should induce the suspicion of REAH.

Antrochoanal Polyps

ACPs are benign lesions originating in the mucosa of the maxillary sinus, which grow within this sinus, up to the choana. Their main symptom is unilateral nasal obstruction and, when compared with nasal polyps, they are generally unilateral and occur in younger patients. Macroscopically, they have an intramaxillary cystic portion and a solid intranasal portion.22 Microscopically, an ACP is similar to a cyst of the maxillary mucosa. According to the study by Maldonado et al.,23 the presence of submucosal glands was significantly less pronounced within the ACP group than within the group of nasal polyps. The histological findings and clinical features of ACP suggest a causal relationship with nasal allergy and a strong association with inflammatory processes. The lack of submucosal glands suggests that ACPs are the result of an oedematous hypertrophy of the respiratory epithelium rather than of the distension of glandular structures.23

Inverted Papilloma

Inverted papilloma (IP) consists of stratified squamous respiratory epithelium. Similarly to REAH, IP is derived from the epithelium of the sinonasal Schneiderian mucosa. It is characterised by a marked thickening of the epithelial layers, while REAH presents an adenomatoid structure of the respiratory epithelium, often in a single layer.

Epithelial proliferation through the thickening of the mucosal cells, intraepithelial mucous cysts and the presence of inflammatory cells in the epithelium are typical of IP. This papilloma can be recurrent and may develop malignant neoplasms (5%-10% squamous carcinomas), which require complete excision.

Adenocarcinoma

Adenocarcinomas arise from the surface of the respiratory epithelium and the seromucous glands of the upper airways. They represent between 10% and 20% of all sinonasal neoplasms and are classified into salivary and non-salivary.24 The difficulty in their differential diagnosis lies in distinguishing cases of REAH with florid mucinous changes from low grade adenocarcinomas originating in the nasal mucosa and paranasal sinuses, especially when only small biopsies are available.25

Adenocarcinomas often consist of a complex glandular growth with cribriform pattern (back-to-back) without stromal tissue. In addition, it is possible to observe individual glands surrounded by an eosinophilic basal membrane. The neoplastic glands are infiltrating and often induce a desmoplastic response by the stroma. It is possible to find a variety of different morphological types of sinonasal tract adenocarcinomas, ranging from low grade (well differentiated) to high grade (poorly differentiated).3 Ingram et al.3 believe that the identification of the stroma between ciliated glands.
**Table 3  Main Differential Diagnoses and Anatomopathological Findings.**

<table>
<thead>
<tr>
<th></th>
<th>REAH</th>
<th>ACP</th>
<th>NP</th>
<th>IP</th>
<th>ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Origin</strong></td>
<td>Two hypotheses:</td>
<td></td>
<td></td>
<td></td>
<td>Unclear: in the superficial epithelium or the epithelium of seromucous glands of the submucosa</td>
</tr>
<tr>
<td></td>
<td>- 1st: congenital hamartomatous proliferations</td>
<td>- Scarce inflammatory infiltrate and scarce eosinophilia</td>
<td>- Infiltration of inflammatory cells, mainly eosinophils, with remodelling and swelling of basal membrane</td>
<td>- Stratified squamous epithelium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 2nd: related to a prolonged pro-inflammatory environment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>- Participation of nasal septum (mainly the posterior part)</td>
<td>- Maxillary sinus</td>
<td>- Ethmoid sinus</td>
<td>- Lateral nasal wall and sinuses</td>
<td>- Nasal fossa, followed by ethmoid and maxillary sinuses</td>
</tr>
<tr>
<td><strong>IHC findings</strong></td>
<td>- Ciliated epithelium positive for CK7</td>
<td>- Expression of MMP-2 incremented by inflammatory cells</td>
<td>- Increased expression of MMP-2 by inflammatory cells</td>
<td>- Coexpression of CK7, CK8, CK19, p63 and HMWK by transitional, non-keratinised squamous cells</td>
<td>- Positive for CK7, CK19 and S100</td>
</tr>
<tr>
<td></td>
<td>- Basal membrane cells positive for p63 and HMWK</td>
<td></td>
<td></td>
<td></td>
<td>- Negative for CK20, CDX2</td>
</tr>
<tr>
<td><strong>Macroscopic characteristics</strong></td>
<td>Oedematous mucosa of the maxillary sinus, growing through the middle meatus and protruding to the choana and nasopharynx</td>
<td>- Tissue oedema appearing more frequently in clefts of middle meatus and prolapse into the nasal cavity</td>
<td>- Polypoid lesions</td>
<td>- Preserved mucosa</td>
<td>- Scarce papillary or granular tissue</td>
</tr>
<tr>
<td><strong>Microscopic characteristics</strong></td>
<td>- Individual glands connected to the surface</td>
<td>- Do not differ significantly from nasal polyps</td>
<td>- Endophytic, inverted growth pattern with scarce extension to stroma</td>
<td>- Tubular, tubulocystic, papillary or micropapillary architecture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Thick basal membrane</td>
<td>- ACP and NP mixed component and covered by pseudostratified epithelium</td>
<td></td>
<td>- Transition surface to the normal mucosa may be present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Multilayered ciliated respiratory epithelium</td>
<td></td>
<td></td>
<td>- Glands in back-to-back arrangement or large cystic adenomatoid glands</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Adenomatoid proliferation</td>
<td></td>
<td></td>
<td>- Cellular atypia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Absence of seromucous glandular component</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACP: antrochoanal polyp; ADC: adenocarcinoma; IHC: immunohistochemistry; IP inverted papilloma; NP: nasal polyps; REAH: respiratory epithelial adenomatoid hamartoma.
in the case of REAH is the most accurate way to diagnose this entity, distinguishing it from low grade carcinomas, which have an aggressive growth, with bone destruction and invasion of soft tissues.

**Conclusion**

Hamartomas are non-neoplastic growths composed of an excessive, albeit localised, proliferation of cells and tissues belonging to a given organ. They are considered as a benign disease of unclear origin. Only about 60 cases located in the nose and the paranasal sinuses have been described in the literature. A correct differential diagnosis with nasal polyps, antrochoanal polyps, inverted papilloma and adenocarcinoma is of vital importance in order to avoid subjecting patients to unnecessary radical therapy. The use of sinonasal endoscopic surgery as a first-line treatment has proven to be safe, effective and curative.

Currently, REAH is a clearly underdiagnosed disease and due to the low number of reported cases, we consider it important to document its casuistry. It can be detected more effectively in clinical practice by increasing awareness of this entity. On the other hand, the role of the pathologist is essential for a correct diagnosis. Consequently, otolaryngologists and pathologists should be familiar with this disease, with the aim of increasing its rates of detection and correct diagnosis, to propose the most appropriate treatment.

**Conflict of Interests**

The authors have no conflicts of interest to declare.

**References**