Respiratory Epithelial Adenomatoid Hamartoma: A Review

Valerie A. Fitzhugh · Neena Mirani

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Abstract Respiratory epithelial adenomatoid hamartoma (REAH) is an uncommon lesion of the upper aerodigestive tract first described by Wenig and Heffner in 1995 as prominent glandular proliferations lined by ciliated respiratory epithelium originating from the surface epithelium. The entity is seen most often in male adults. Clinically the lesion presents as a polypoid mass, often in one or both nasal cavities, though other locations have been described. While REAH is benign, awareness and recognition of the lesion is important because it can be easily confused grossly and microscopically with more threatening tumors such as inverted papilloma and sinonasal carcinoma. The literature of REAH is reviewed with detail paid to the histologic diagnosis. The clinical presentation, radiologic findings, and differential diagnosis are also described.

Keywords Respiratory epithelial adenomatoid hamartoma · Inverted papilloma · Sinonasal adenocarcinoma · Nasopharynx · Upper aerodigestive tract

Introduction

Hamartomas are defined as aberrant differentiation which may produce a mass of disorganized but mature specialized cells or tissue indigenous to the particular site [1]. These lesions are benign. Unlike neoplasms, hamartomas lack the

ability to grow continuously, resulting in a self limited proliferation [2–4]. Hamartomas tend to originate from the lung, liver, spleen, kidney, and intestine, but uncommon examples have been noted in the upper aerodigestive tract [5].

Respiratory epithelial adenomatoid hamartoma (REAH) was first described in a series of 31 cases by Wenig and Heffner in 1995 [2]. Before 1995, only 13 cases of nasal hamartoma had been reported. The bulk of the cases that have been reported have been in males in the third to ninth decades of life [2, 6]. These masses occur in the nasal cavity, paranasal sinuses, and nasopharynx [2–11].

To date, there is limited literature regarding REAH, and the majority has been published as case reports [3, 4, 6–16]. Recent publications have expanded on the immunohistochemical and molecular genetic features of these lesions, which have assisted in their greater understanding [17, 18]. The challenge of this lesion is to not overdiagnose it as malignant because it can be treated with a simple excision as opposed to radical surgery. This review will include the clinical, histopathologic, immunohistochemical, and molecular genetic features of REAH as well as a discussion of the differential diagnosis.

Clinical Features

REAH is a benign lesion predominantly affecting men in the third to ninth decades of life. The male-to-female ratio is roughly 7:1 [2, 7]. To date, 60 cases have been reported in the literature confirming the uncommon nature of this proliferation [2–4, 6–8]. Presenting complaints include nasal obstruction, nasal stuffiness, deviated septum, epistaxis, rhinorrhea, chronic recurrent sinusitis, facial pain, proptosis, and hyposmia [2–4, 6–9]. In one case the presentation was a periapical mass on routine dental examination.

V. A. Fitzhugh (✉) · N. Mirani
Department of Pathology and Laboratory Medicine, University
of Medicine and Dentistry of New Jersey-New Jersey Medical
School, University Hospital-E-156, 150 Bergen Street, Newark,
NJ 07103, USA
e-mail: valerie_a_fitzhugh@comcast.net

On radiologic studies, this mass was a periapical lucency [10]. These symptoms have been seen to occur for a few months up to as many as 8 years [2]. The most common identified site of occurrence is the nasal cavity, specifically the posterior septum [2–4, 6–9]. The lesion bears no right or left side predilection and often involves both nasal cavities [2].

Radiologically, the most common finding of REAH is an opacification of the affected sinus and some connection to the nasal septum [3, 4, 6, 7]. The lesion also tends to grow slowly, as evidenced by bony expansion rather than erosion [7]. Lima et al. [14] attempted to demonstrate that REAH causes enlargement of the olfactory clefts, a finding seen on computed tomography (CT) scans. They reviewed the axial and coronal CT images of 15 patients with REAH, 36 patients with nasal polyposis, and 49 individuals without disease of the sinuses. They found that REAH indeed significantly enlarges the width of the olfactory cleft, and in patients with bilateral disease, this difference is important in the differential diagnosis with nasal polyposis [14].

Many cases of REAH arrive as a biopsy. It is important to consider this diagnosis as the definitive treatment for REAH is a simple surgical excision while the other diagnoses require more complex surgical excision. Another favorable characteristic of REAH is that complete excision is curative, lending to an excellent prognosis [2–13, 15]. Some cases have been followed for as many as 5 years post excision without evidence of recurrence [2, 3, 9, 11]. A summary of the reported cases of REAH is given in Table 1.

Pathologic Findings

Gross Pathology

REAH tends to have a polypoid appearance. The polyps tend to be fleshy to firm, yellow to white masses of varying sizes. Some lesions have a glistening, edematous appearance [5]. Other authors have reported an elastic quality to these lesions [6]. The largest lesion reported thus far attained 5 cm in greatest dimension [19]. The cut surface also tends to be yellow and firm with areas of induration noted.

Histologic Features

The histologic picture is dominated by the presence of a glandular proliferation with a polypoid appearance. The proliferation tends to be submucosal (Fig. 1) [2, 19]. The glands are lined by ciliated respiratory epithelium originating from the surface respiratory epithelium [2]. The glands are typically round to oval in shape and were small to medium in size with prominent dilation. Stromal tissue separates the glands, and complex glandular growth and cribriform architecture is absent [2]. The epithelium may be cuboidal or flat, and mucinous gland metaplasia is often seen (Fig. 2) [2, 19]. Occasionally the gland lumina are filled with mucinous or eosinophilic amorphous material. Stromal hyalinization may be seen, but is not present in all cases [2].

Other histologic features described include stromal edema, polypoid growth, seromucinous gland proliferation,

Table 1 Summary of reported cases of respiratory epithelial adenomatoid hamartoma

Source	No. of male patients	No. of female patients	Age (year)	Biopsy before resection (Y/N)	Surgical resection (Y/N)	Follow-up period	Recurrence (Y/N)
Wenig and Heffner [2]	27	4	27–81	Information not given.	Y in all 31 cases	4 months–5 years	N in all 31 cases.
Endo et al. [3]	1	0	65	Y	Y	2 years	N
Delbrouck et al. [4]	0	1	79	N	Y	Information not given	N
Ingram et al. [6]	1	0	54	N	Y	Information not given	Information not given
Athre et al. [7]	0	1	66	N	Y	Information not given	N
Flavin et al. [8]	1	0	11	N	Y	6 months	N
Himi et al. [9]	1	0	56	Y	Y	1 year	N
Kessler and Unterman [10]	0	1	57	N	Y	Information not given	Information not given
Metselaar et al. [11]	0	1	68	Y	Y	13 months	N
Malinvaud et al. [12]	1	0	74	N	Y	15 months	N
Roffman et al. [13]	1	2	56–80	Y in 2 cases N in 1 case*	Y	3 months–1 year	N
Braun et al. [15]	0	1	51	N	Y	6 months	N

* A bilateral excisional biopsy was performed in this case

Fig. 1 Respiratory epithelial adenomatoid hamartomas are composed of prominent glandular structures of varying sizes

Fig. 2 The glands are lined by ciliated respiratory epithelium. The nuclei are bland. Note the mucinous gland metaplasia

acute and chronic inflammation including neutrophils, eosinophils, lymphocytes, plasma cells, and histiocytes and vascular and fibroblastic proliferation [2, 19]. Dysplastic and neoplastic changes are not seen. Inverted papillomas and solitary fibrous tumor have been seen in association with REAH [2, 19].

The nuclear features of REAH are bland. Prominent nucleoli are rare, as are mitoses. These findings support the benign nature of the lesion. Long term chronic inflammation and polyp formation within the respiratory epithelium are thought to be the etiologic precursors to REAH, which helps to explain chronic sinusitis as a presenting symptom in this process [2, 7, 9].

Lastly, there are two reports of cases with chondro-osseous differentiation [8, 13]. Wenig and Heffner [2] observed cases in their original study which showed osseous metaplasia, but did not initially classify the

mesenchymal component. They later wrote an abstract defining this subtype. Flavin et al. [8] published the first case report of chondro-osseous respiratory adenomatoid hamartoma (COREAH). The histological features were almost exactly the same as REAH. In addition, however, COREAH has islands of cartilage interspersed throughout the lesion [8]. A second case of COREAH is described by Roffman et al. [13].

Immunohistochemistry

Immunohistochemistry has not been used to an extensive degree in the diagnosis of REAH. Before early 2007, only one group had attempted to use any type of immunohistochemistry in their workup of the lesion [3]. It was thought that the use of MIB-1 could be useful in distinguishing REAH from other neoplasms, particularly inverted papillomas and sinonasal adenocarcinomas. In that report, less than 1% of the ductal cells in the lesion were positive for MIB-1. The authors indirectly suggested that the lesion, based on this evidence, is more likely to be a hamartoma than a neoplasm, since neoplasms tend to have a high proliferation index [3].

Before 2007, no one had attempted to develop an immunohistochemical profile for REAH, as the proliferation is diagnosed largely on morphologic grounds. However, Ozolek et al. [17] introduced an immunohistochemical study in which they examined the profile of REAH. They examined an immunohistochemical panel including cytokeratin (CK) 7, CK20, 34 β E12, CDX-2, p63, KI-67 (MIB-1), smooth muscle actin (SMA), S-100 protein and calponin. p63 staining was seen in the basal cells of REAH, which had a low proliferation index. REAH was also seen to be CK7 positive and CK20 and CDX-2 negative. This information may prove invaluable in the differential diagnosis of REAH, which will be discussed later.

Molecular Genetics

To date, there is only one study which has examined the molecular genetics of REAH. Ozolek and Hunt [18] noted that a few studies had addressed the molecular changes in sinonasal adenocarcinomas, especially the intestinal type, but no one had tackled the molecular genetic changes in REAH. They felt that examining the tumor suppressor gene profiles of REAH could lead to better classification of the lesion.

In Ozolek and Hunt's study [18], 10 cases of REAH, 9 cases of sinonasal carcinoma, and 10 cases of chronic sinusitis were microdissected and the DNA was amplified via polymerase chain reaction (PCR). The products analyzed were genes on chromosomes 9p (CDKN2/p16), 11p

(H-ras), 17p (p53), and 18q (DCC/DPC4) [18]. The products were analyzed by capillary electrophoresis. REAH was shown to have high loss of heterozygosity (LOH) for the loci located on chromosomes 9p and 18q. It also exhibited a fractional allelic loss (percentage of loci that harbored LOH/number of informative loci) of 31%, which the authors concluded was unusually high for a non-neoplastic entity [18]. The authors concluded that REAH may in fact be a benign neoplasm and not a hamartoma as was originally believed.

The molecular genetics of REAH is in its infancy. It will be essential for other authors to build upon this landmark study in order to confirm or refute the results and to give them further meaning in the realm of surgical pathology.

Differential Diagnosis

Inflammatory Polyp

The first differential diagnosis of REAH is the inflammatory polyp (Figs. 3, 4) [2, 5, 10]. In cases where there is a lack of a florid adenomatoid proliferation, REAH can be misdiagnosed as an inflammatory polyp because of the overlap of the clinical, morphologic, therapeutic, and biologic features [10]. One of the most notable clinical differences between REAH and inflammatory polyps is the location, in that the bulk of REAHs involve the posterior nasal septum [2, 4, 5]. The gross appearances are also quite different, with REAH showing a predilection for induration [2, 4, 5]. Both lesions can show fibroblastic and vascular proliferation, stromal edema, a mixed inflammatory cell infiltrate, and seromucinous gland proliferation [2, 5]. However, inflammatory polyps do not have florid adenomatoid proliferation and stromal hyalinization which, when

Fig. 3 Inflammatory polyp with edematous inflammatory stroma and single layered glands

Fig. 4 High power of inflammatory polyp showing inflammatory stroma without hyalinization and a single layered gland without the typical features of REAH

present, favor REAH. Care must be taken when evaluating these lesions.

Inverted Papilloma

Inverted papillomas, or the inverted type of Schneiderian papillomas, are the second differential in the diagnosis of REAH. Unlike inflammatory polyps and REAH (at this time), inverted papillomas are considered true neoplasms and require more extensive surgical excision to remove the tumor and possible dysplastic foci [2, 5]. Clinically, these neoplasms have the capacity to destroy bone, extend along mucosal surfaces, and invade the adjacent vital structures, which is of concern in the vessel-rich nasal cavity and sinuses [2, 5].

Inverted papillomas arise from the invagination of stratified squamous epithelium (Fig. 5). The inverted growth of squamous epithelium is not seen in REAH. Histologically, inverted papillomas are comprised of proliferating squamous epithelial cells with an admixture of mucin containing cells and microcysts. Occasional mitoses may be seen in the basal layer, and there is usually mild to moderate atypia [20]. While REAH tends to be located in the posterior nasal septum, inverted papillomas have a predilection for the lateral wall of the nasal cavity, and in addition to their locally aggressive clinical behavior also have the potential to recur [20]. These neoplasms also have the potential for malignant transformation which to date has not been described in REAH.

In some cases, histologic examination may reveal the surface component of an inverted papilloma to be composed of respiratory type epithelium similar to that seen in REAH. It has been recommended to not use this as a distinguishing feature and instead to observe the proliferating

Fig. 5 Inverted papilloma originating from overlying squamous epithelium. Note the respiratory epithelial changes that one could confuse with REAH

epithelium for marked thickening with mucocytes, intra-epithelial mucous cysts, and the presence of inflammatory cells streaming through the epithelium. These findings are more specific for inverted papillomas [2, 5, 10]. Furthermore, the lining epithelium of REAH tends to be a single cell layer, assisting in the diagnosis [5, 10].

Sinonasal Adenocarcinoma

Sinonasal adenocarcinoma is the third differential diagnosis for REAH. It accounts for approximately 20% of all sinonasal malignancies and is classified into salivary and nonsalivary types [5, 20]. Adenocarcinomas without a specific salivary gland tumor pattern usually arise on the middle turbinate or in the ethmoid sinus; from there it extends laterally into the orbit and upward into the anterior cranial fossa [20]. These neoplasms seem to arise from the mucosal lining of the sinuses rather than the glandular component.

On microscopic examination, sinonasal adenocarcinomas show a wide range of differentiation and patterns. Intestinal type adenocarcinomas are of high grade. The most common architecture is the tubulopapillary type but goblet cell, signet ring, and mucinous types have been described (Fig. 6) [5, 20]. In very rare cases a neuroendocrine component may be seen [20]. Differentiating the intestinal type sinonasal adenocarcinoma from REAH is usually not difficult as the cell types, high grade features, and greatly increased mitoses are features of adenocarcinoma [5].

Low grade adenocarcinomas, on the other hand, can originate from the surface epithelium as well as from the seromucinous glands of the submucosa [5]. Classically, oncocytic papillomas can be confused with low grade

Fig. 6 Sinonasal adenocarcinoma, low power

adenocarcinomas, but today, REAH has entered that differential diagnosis as well. While there are guidelines for distinguishing oncocytic papillomas from low grade adenocarcinoma, there are no guidelines to date for distinguishing REAH (especially those with a metaplastic mucinous component) from low grade sinonasal adenocarcinoma [5]. This difficulty is enhanced if the specimen submitted is a small biopsy specimen. Sangoi and Berry propose features that may allow for differentiation of REAH from low grade sinonasal adenocarcinoma, including absence of cribriform architecture, individual glands surrounded by eosinophilic basement membranes, and the presence of ciliated epithelium lining expanded lumens filled with mucin [5]. Furthermore, REAH does not show the features of adenocarcinoma including nuclear stratification, dysplasia, and increased mitotic rate [20].

These adenocarcinomas are locally aggressive tumors. The low grade type is surprisingly aggressive despite its well differentiated appearance. Lymph node metastases are rare [20].

Immunohistochemistry and Differential Diagnosis

As stated earlier, the immunohistochemistry of REAH is in its infancy. However, the study performed by Ozolek et al. [17] offers some guidance as to how to approach these lesions. In their study, some important differences were established. Ki-67 can be used as an index of proliferation, with REAH showing intermediate proliferation and sinonasal adenocarcinomas showing high proliferation [17], a result which would be expected. While REAH and inverted papilloma showed CK7+, CK20–, only sinonasal carcinoma was CK20+. CDX-2 positivity was also demonstrated only in sinonasal carcinomas as well. Again, this study is most likely a starting point for further clarification of the immunohistochemical profile of REAH.

Conclusion

Respiratory epithelial adenomatoid hamartoma truly is a lesion in its infancy. Described only a decade ago, it is an uncommon entity with distinctive morphologic features. Clinically, it is an expansile mass which causes upper respiratory symptoms and discomfort mainly in adult men, although cases in women and children have been reported. Distinctive histologic features include a glandular component which originates from the overlying surface respiratory epithelium and polypoid growth as a result of respiratory epithelial adenomatoid proliferation. The columnar cells lining the glands are ciliated, further illustrating the benign nature of the lesion. Diagnostic misinterpretation is a serious issue regarding this lesion. Pathologists must be aware of this entity in order to avoid overdiagnosis and excessive surgical procedures for the patient.

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