LITERATURE REVIEW

Respiratory epithelial adenomatoid hamartoma: a few considerations and a review of literature

Alina Anda Nagy, Veronica Trombitas, Diana Vlad, Silviu Albu

II-nd Department of Otolaryngology, University of Medicine and Pharmacy Cluj-Napoca, Cluj-Napoca, Romania

ABSTRACT

Respiratory Epithelial Adenomatoid Hamartoma (REAH) is a rare entity arising in the sinonasal tract, which was first described by Wenig and Heffner in 1995. REAH is characterized by glandular proliferation lined by respiratory cilliated epithelium, enveloped by a thick basement membrane and stromal hyalinization. It presents as a polypoid mass of the nasal cavity, nasopharynx or paranasal sinuses and it can be unilateral or bilateral, isolated or associated, most commonly with sinonasal polyps. REAH is invariably benign and complete surgical resection is curative, hence the importance of recognizing and differentiating REAH from other potentially more aggressive lesions of the sinonasal tract, like inverted papilloma and adenocarcinoma.
Given the rarity of sinonasal hamartomas, the literature regarding REAH is limited and it consists primarily of case reports with only a handful of case series describing this particular lesion since the initial series presented by Wenig and Heffner.
This article reviews the available literature on the subject, with emphasis on demographics, clinical features, histology, differential diagnosis and management of REAH.

KEYWORDS: hamartoma, nasal cavity, nasal polyps, papilloma, adenocarcinoma

INTRODUCTION

Hamartomas are noncancerous tissue masses comprised of disorganized specialized cells indigenous to the particular area of the body where they occur. The cells are normal for the given anatomic site, but are abnormal in amount or distribution, with an excess of one or more tissue types. Hamartomas arising in the head and neck are very rare and those of the sinonasal tract are exceedingly uncommon. Of special interest among hamartomas of the head and neck is the Respiratory Epithelial Adenomatoid Hamartoma (REAH).

Respiratory Epithelial Adenomatoid Hamartoma was first described and characterized as a distinct entity by Wenig and Heffner in 1995[1] and was included in the World Health Organization (WHO) Classification of Head and Neck Tumors in 2005[2]. REAH occurs in adult patients, the median age of diagnosis being situated in the sixth decade, with predominance in males. It arises in the nasal cavities with predominance for the posterior nasal septum[2], but other sites such as the paranasal sinuses, nasopharynx and olfactory cleft have also been reported[3]. Most REAH appear to be isolated lesions, but bilaterality has been reported[2,3]. REAH often arises in an inflammatory setting and it is detected in conjunction with inflammatory polyps[2]. Morphologically, REAH appear as polypoid or exophytic lesions with tan-white, yellow-pink to red-brown coloring, a glistening surface and a rubbery consistency[1,2]. These lesions are invariably benign and complete surgical resection is curative with very few recurrences, hence the importance of recognizing and differentiating REAH from other potentially more aggressive lesions of the sinonasal tract.

Given the rarity of sinonasal hamartomas, the literature regarding REAH is limited and it consists primarily of case reports with only a handful of case series on this particular lesion since the initial series presented by Wenig and Heffner.

This article reviews the available literature on the subject with emphasis on demographics, clinical features, histology, differential diagnosis and management of REAH.

Corresponding author: Silviu Albu, MD, Professor of Otorhinolaryngology, II-nd Department of Otolaryngology, University of Medicine and Pharmacy Cluj-Napoca, 18 Republicii Street, 3400 Cluj-Napoca, Romania
email: silviualbu63@gmail.com

DISCUSSIONS

REAH was first individualized as a distinct entity by Wenig and Heffner in 1995[1], when they reported a series of 31 cases involving the nasal cavities and nasopharynx and they described the clinicopathological features of this newly discovered lesion with emphasis on the age of diagnosis, male to female ratio, presenting symptoms, location within the sinonasal tract, morphology, both macroscopic and histologic, management and outcome. The authors did not mention whether the lesions were unilateral or bilateral. Since Wenig's study reports on the subject have been limited to a handful of case series and case reports, in 2006 Lima et al.[4] published a retrospective study in which he compared the Computed Tomography (CT) images of 15 REAH patients to those of patients with Sinonasal Polyps (SNP) and to CT scans with no sinonasal pathology, establishing the radiographic treats suggestive of REAH. In addition, they offered information regarding demographics and clinical features. The largest study of REAH to date is the one reported by Vira et al. in 2011[5], who presented a retrospective series of 54 patients treated with endoscopic resection over a 10-year period. The cases were incidental findings discovered over routine histologic processing of surgical specimens obtained during Functional Endoscopic Sinus Surgery (FESS), and no pathognomonic symptoms or distinguishing radiographic features to suggest REAH were noted. Most recently, Hawley et al.[6] published a retrospective study on a cohort of 45 cases of REAH, diagnosed between 2006 and 2011, with emphasis on clinical presentation, histologic and radiographic features and Lee et al.[3] reported in 2013 a series of 51 cases of REAH describing age, gender, clinical presentation, histologic findings, treatment and outcomes and also radiographic treats suggestive of REAH, completed with measurements of the olfactory cleft (OC) as previously performed by Lima[4]. Although REAH is considered a non-neoplastic entity, a recent molecular genetics study published by Ozolek and Hunt showed a high loss of heterozygosity and a fractional allelic loss that was unusually high for non-neoplastic entities. These findings led the authors to conclude that REAH is a benign neoplasm rather than a hamartoma[7].

Demographic Data

The majority of REAH occur in adults with ages ranging from the third to eighth decade and a median age situated in the sixth decade. Reported ages at diagnosis range from 23 years to 93 years[1,3,4,6], with a median age of 52 to 58.4 years[1,3-6], with a few reports on small series of patients with a median age of 62 to 65 years[8,9]. Most reports though are in concordance with the initial data regarding the age of diagnosis provided by Wenig and Heffner. There are, however, reports of REAH in younger patients, namely the case of a 9-year-old boy presenting with REAH of the anterior nasal septum[10].

Initially, Wenig and Heffner reported a clear male predominance, with male to female ratio of almost 7 to 1[1]. Later studies reported relatively equal distribution among sexes[4-6,8]. Lee et al. reports a predominance of REAH in males, with 37 males to 14 females within the series[3].

Clinical presentation

The primary presenting symptoms of REAH consist of nasal obstruction[1,3,4,6], nasal congestion, and hyposmia/ anosmia[1,3,4]. Other symptoms include headache, rhinorrhea, facial pressure, postnasal drip or epistaxis[1,3,6], depending on the location of the lesion. Less common presenting symptoms consist of proptosis[1,11] and ear plugging, reported by Lee et al.[3] in one case of their series. There is one reported case which presented with a periapical mass on routine dental examination[12]. Also, several cases represent incidental findings, diagnosed upon pathologic examination. Such was the case of Vira's cohort[5] in which, as mentioned before, the diagnosis of REAH was established upon pathologic examination of surgical specimens. Moreover, the discovery of REAH was incidental for 33 of the 45 patients reported by Hawley et al.[6] and Lee et al.[3] report that preoperative diagnosis of REAH was made in only 5.9% of cases, the rest of 94.1 % cases being discovered incidentally upon pathologic examination.

On endoscopic evaluation, REAH appear as polypoid or exophytic masses with tan-white, yellow-pink to red-brown coloring, with a glistening surface, usually darker and with a firmer consistency than sinonasal polyps[1,3]. They appear in varying sizes from a few millimeters up to six centimeters in diameter[1].

REAH generally present as isolated lesions or in association with other sinonasal pathologies. Most of the cases reported by Wenig et al.[1] were isolated lesions (29/31), only two cases presenting with concurrent pathologies, one of them with Schneiderian papilloma, inverted type, and the other presenting a fibrous tumor. These associations were interpreted by the authors as coincidental. By contrast, all cases presented by Vira et al.[5] had associated pathologies: chronic rhinosinusitis was present in 44 (81%) cases, sinonasal polyps in 9 (17%) cases and 1 (2%) presented with allergic sinusitis. 33 patients of Hawley's 45 case cohort presented with associated lesions, the majority of them with associated sinonasal polyps (26/33), the others with Schneiderian papilloma, inverted type (2/33), malignant lesions (3/33), adenoiditis (1/33) and hereditary hemorrhagic telangiectasia (1/33)[6]. In Lee's study[3], 68% (35/51) of the reported cases had associated inflammatory pathologies, most of them

(20/35) presented with associated sinonasal polyps, chronic rhinosinusitis was observed in 12/35 cases and allergic fungal sinusitis was reported in 3/35 cases.

Historically, REAH has been described to most commonly arise from the nasal cavities. In Wenig's cohort, the majority of cases (71%) were identified in the nasal cavities with a predilection for the posterior nasal septum. However, later studies tend to contradict the initial reports. Vira et al. observed REAH most frequently affecting the sinuses (85%) rather than the nasal cavities (15%)[5]. The latter originated from the nasal septum, middle turbinate and inferior turbinate. Hawley et al. reported that isolated REAH displayed a predilection for the olfactory clefts (75%; 9/12) as opposed to the nasal septum (15%) as site of origin[6]. Lee et al.[3] confirm the olfactory cleft as the primary site of origin for isolated REAH with 56.2% (9/16) cases, while the remaining 43.8% (7/16) were situated in the posterior nasal septum and nasopharynx.

Bilaterality has recently been noted as a rather common occurrence. Lee et al.[3] note that 37.3% (19/51) of cases were bilateral, whereas Hawley observed bilaterality more frequently in isolated REAH (8/12 cases) with a predilection for the olfactory cleft.

Radiologic findings

Imaging studies commonly reveal an opacification connected to the nasal septum with opacification of the adjacent paranasal sinuses (see Figure 1), especially for unilateral lesions[11,13-15]. It has been recognized that the computed tomography scans of bilateral disease display a characteristic widening of the olfactory clefts, trait that is essential in distinguishing REAH from sinonasal polyps[16,17]. In 2006, Lima et al. observed and described for the first time the widening of the olfactory clefts as a characteristic feature for REAH[4]. A statistically significant widening of the olfactory clefts was evident, especially in the anterior half, when comparing the REAH tomographic images with those of sinonasal polyps and to normal scans, and lateralization of the middle turbinate and narrowing of the ethmoidal space were also observed[4]. Hawley et al. report the widening of the olfactory clefts as a characteristic radiographic trait for isolated REAH both unilateral and bilateral[6].

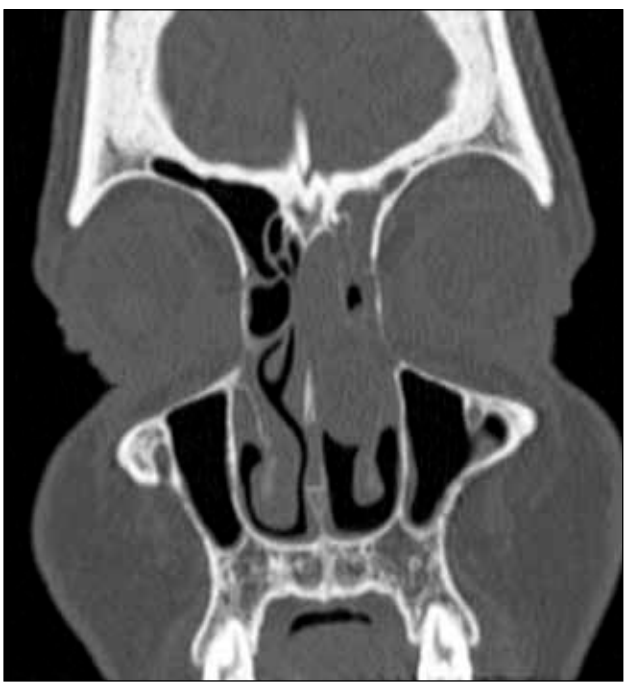

Figure 1 CT scan of the paranasal sinuses displaying opacification of the left ethmoid sinus

In an earlier case control study, Hawley observes the enlargement of olfactory clefts in both isolated REAH and REAH associated with sinonasal polyps when compared to a control group consisting of patients with sinonasal polyps[18]. The report of Lee et al.[3] regarding the width of the olfactory clefts is concurrent with the findings reported by Lima and Hawley, with the mention that the olfactory cleft width for REAH cases is smaller in Lee's cohort when compared to Lima's results; the former attributes this discrepancy to the anatomical difference, noting that Lima's cases consisted of solely isolated bilateral lesions that involved the olfactory clefts, whereas their own cohort consisted of both isolated and associated REAH primarily arising from the posterior septum[3].

Histologic features

REAH is characterized by submucous glandular proliferation of pseudostratified ciliated columnar epithelium that originates from the surface respiratory epithelium (Figures 2 and 3), often admixed with goblet cells[2,19]. The glands are small to medium in size, round to oval in shape and are often in direct contact with the surface epithelium. They are often dilated and the gland lumina is filled with mucus or eosinophilic amorphous material[2,3]. The glands are back-to-back, separated by minimal stromal tissue and enveloped by a thick eosinophilic basement membrane. Stromal hyalinization is characteristic to REAH, but is not present in all cases. Stromal edema, seromucinous gland proliferation, stromal mixed inflammatory cells and vascular and fibroblastic proliferation have also been observed in REAH[19]. Complex glandular growth and cribriform architecture are absent[20], mitoses are rare and nuclear atypia is absent[3].

Chondro-osseous differentiation, consisting of islands of cartilage or bone within the REAH, presently known as condro-osseous REAH (COREAH), has been reported in a limited number of cases[8,21]. Weinreb notes that the cartilage and bone are normal and questions whether the condro-osseous component is part of the lesion or these islands are actually normal structures entrapped by the proliferation[19].

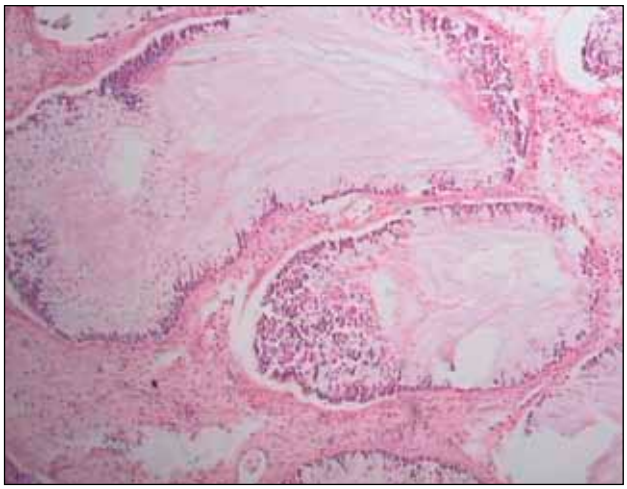

Figure 2 Histological examination of respiratory epithelial adenomatoid hamartoma

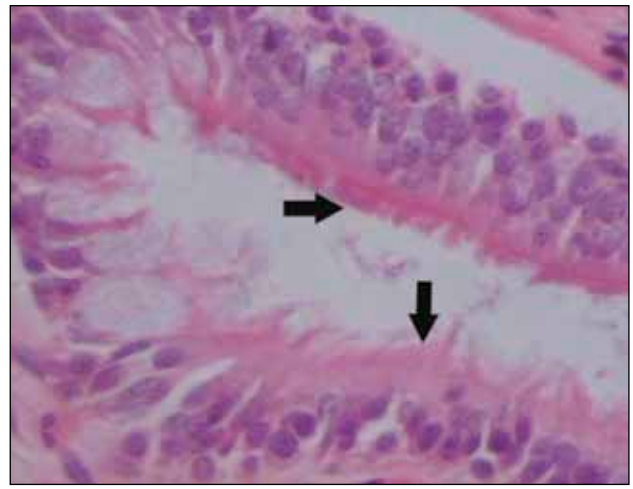

Figure 3 REAH: glands lined by ciliated respiratory epithelium

Immunohistochemistry for REAH is not commonly used for diagnosis, but could potentially play a major role in differential diagnosis. The first study on the subject was published by Ozolek in 2007. He aimed to determine the immunohistochemical profile of benign and malignant glandular lesions of the sinonasal tract. He concluded that the epithelial components were positive for cytokeratin (CK)[7], the basal cellular layer surrounding the deep glands was uniformly positive for p63, 34βE12 (weaker cytoplasm staining was also present), and Ki-67 (present solely in the basal layer and demonstrated the lowest proliferation index of any group of lesions included in the study). CK20, CDX-2, calponin, S-100 and SMA staining were negative for REAH[22].

Differential diagnosis

The sinonasal tract is the site of a diverse array of pathologies from reactive inflammatory ones, like sinonasal polyps to benign neoplastic and malignant entities. While the most common diagnoses among the entities that arise in the sinonasal tract are inflammatory polyps and papillomas[23], occasionally, differential diagnosis between inflammatory or benign and malignant lesions can be a challenge due to limited bioptic specimens and overlapping features. The differential diagnosis of REAH includes other polypoid masses (unilateral and bilateral) and entities characterized by glandular proliferation, especially the low-grade lesions. It is of high importance that REAH is differentiated from more aggressive entities like Inverted Papilloma and Adenocarcinoma, lesions that require a more aggressive surgical approach.

Sinonasal polyps are a frequent occurrence associated with REAH. When the polypectomy specimen yields glandular proliferation upon histologic examination, REAH should be suspected. Histologically, polyps display stromal edema and stromal mixed inflammatory cells are similar to REAH, but lack glandular proliferation. The basal membrane can be thickened and eosinophils can dominate the inflammatory infiltrate. The primary feature that differentiates REAH from sinonasal polyps is the extensive glandular proliferation. In addition, REAH is more indurated than sinonasal polyps. Also, enlargement of the olfactory crest shown on CT scans of bilateral polypoid masses should raise suspicion of REAH[3,4].

Seromucinous hamartoma is a rare entity that arises in the sinonasal tract. Since it was first described, only a handful additional case reports and case series have been published. It presents as a polypoid mass that involves primarily the posterior nasal septum and nasopharynx, but it can also arise in the lateral nasal wall[19]. No cases involving the paranasal sinuses have been reported to date. The presenting symptoms are similar to other benign lesions of the sinonasal tract. Histologically, the lesion displays lobular or haphazard proliferation of tubules and glands composed of serous cells with eosinophilic cytoplasm, covered by respiratory surface epithelium[19]. Most lesions display focal REAH- like features or even areas of classic REAH and the serous glands have been observed to "bud" from these REAH-like glands[19]. On immunohistochemical examination, the seromucinous lesions are positive for CK7 and negative for CK20 similar to REAH. Unlike REAH, they stain for S100 and are negative for p63 and 34βE12[19]. Weinreb remarked that as the serous glands "bud" from the REAH-like glands, they begin to stain for S100 and lose the basal layer. The histology of seromucinous hamartomas, together with the primary presenting symptoms and location within the sinonasal tract, similar to REAH and the lesions displaying both REAH and seromucinous hamartoma features, prompted Weinreb to consider that REAH and seromucinous hamartoma represent different stages of a spectrum of progression rather than distinct entities[19].

Inverted Papilloma shows similar back-to-back nested glandular architecture similar to REAH. The multistratified epithelium characteristic to inverted papilloma, as opposed to the pseudostratified columnar epithelium seen in REAH, is the primary feature that differentiates the two entities. The epithelial multilayering can be evident only focally in inverted papilloma, but when papilloma-like and REAH-like areas are observed within the same specimen, the papilloma-like areas prevail when making a diagnosis[19]. In addition, the intraepithelial neutrophil infiltrate seen in inverted papilloma is absent in REAH and inverted papilloma lacks the thick basement membrane characteristic to REAH.

The distinction between these two entities is of high importance, as inverted papilloma can be recurrent and they appear to be precursor lesions to squamous carcinoma (the reported association between the two is as high as 10%[23]).

Adenocarcinomas comprise 10%-20% of primary malignant neoplasms and are categorized as salivary type and non-salivary type[23]. The non-salivary group is classified as intestinal type, low and high grade, and non-intestinal type, low and high grade. Adenocarcinomas are characterized by a complex glandular growth with cribriform architecture than can resemble the glandular architecture of REAH, and occasionally the individual glands are enveloped by a thick eosinophilic membrane. The differential diagnosis problems appear when distinguishing REAH from low grade adenocarcinomas arising from the sinonasal tract, especially when the bioptic specimens are small. The salivary type adenocarcinomas are similar to their salivary gland counterparts and are easily distinguished from hamartomas. The intestinal type adenocarcinomas resemble intestinal epithelium, have a predilection for the ethmoid sinus and are associated with wood dust exposure. They may have a papillary architecture or solid growth patterns that are not characteristic to hamartomas. Immunohistochemical staining is positive for CK20 and CDX-2, a feature that is not present in REAH. The low grade non-intestinal-type adenocarcinomas are the most important lesions to be distinguished from REAH due to their aggressive behaviour. They can be invasive or circumscribed and display cribriform or papillary architecture. The glands are back-to-back or coalescent with minimal intervening stroma and are lined by a single layer of cuboidal or cylindrical cells that can occasionally have a pseudostratified appearance[23]. They have a low mytotic index and nuclear atypia, and necroses are absent. Low grade non-intestinal-type adenocarcinomas stain for CK7 and often for S100 and are negative for CK20, CDX2[19]. The absence of ciliated respiratory cells of the thick eosinophilic basement membrane and the presence of submucosal invasion differentiate low grade adenocarcinomas from REAH, although the bland histological appeareance of these tumors makes the distinction problematic.

Treatment and outcome

REAH is reported to be self-limited, with extremely rare recurrences[1,3,5]. Complete surgical resection is curative, usually performed via endoscopic sinus surgery. When REAH is located in the olfactory cleft, special care should be taken in order to prevent the perforation of the cribriform plate and its subsequent complications. In the extremely rare cases with orbital or skull base extension, open cranio-facial surgery and reconstruction could be necessary[3].

CONCLUSIONS

REAH is a rare and unique entity with distinctive morphologic features. Clinically, it presents as a tissue mass that causes upper respiratory obstruction and discomfort. Initially, a clear male predominance was reported, but recent studies show a rather equal distribution. REAH can be unilateral or bilateral, isolated or associated. The most common association is with sinonasal polyps and a significant number of REAH cases are diagnosed upon histologic examination of polypectomy specimens. The downfall of this association though is that REAH can be overlooked and undiagnosed in favour of the more common sinonasal polyps. The clinical presentation and radiologic findings, especially the enlargement of the olfactory clefts on CT scans, are suggestive, but the diagnosis of REAH is made upon histologic analysis. Histologic diagnosis can be challenging, especially if the bioptic specimens are small and REAH can be easily mistaken for other more common and more aggressive entities that arise in the sinonasal tract. Immunohistochemical staining can be helpful in making an accurate diagnosis. REAH is relatively recently described and there are still a few variables regarding this entity.

The hamartomatous nature of REAH has recently been questioned by molecular genetics and REAH shares similar features with both inflammation and tumors of the sinonasal tract.

Therefore, further research is needed to determine the origin, pathophysiology and whether there is a causal or temporal relation between REAH, sinonasal inflammatory conditions and neoplasies.

Acknowledgement

This paper was published under the frame of the European Social Fund, Human Resources Development Operational Program 2007-2013, project no. POSDRU/159/1.5/S/138776.

REFERENCES

1. Wenig B.M., Heffner D.K. - Respiratory epithelial adenomatoid hamartomas of the sinonasal tract and nasopharynx: a clinico- pathologic study of 31 cases. Ann Otol Rhinol Laryngol., 1995;104:639-645.
2. Wenig B.M. - Respiratory Epithelial Adenomatoid Hamartoma. In: Barnes L., Eveson J.W., Reichart P., Sidransky D., editors. - World Health Organisation Classification of Tumours. Pathology and Genetics of Head and Neck Tumours. IARC Press, Lyon, 2005;p.33.
3. Lee J.T., Garg R., Brunworth J., Kreschner D.B., Thompson L.D.R. - Sinonasal respiratory epithelial adenomatoid hamartomas: Series of 51 cases and literature review. Am j Rhinol Allergy., 2013;27:322-328.
4. Lima N.B., Jankowski R., Georgel T., Grignon B., Guillemin F., Vignaud J. - Respiratory adenomatoid hamartoma must be suspected on CT-scan enlargement of the olfactory clefts. Rhinology, 2006;44 (4):264-269.
5. Vira D., Bhuta S., Wang M.B. - Respiratory epithelial adenomatoid hamartomas. The Laryngoscope, 2011;121:2706–2709.
6. Hawley K.A., Pabon S., Hoschar A.P., Sindwani R. - The presentation and clinical significance of sinonasal respiratory epithelial adenomatoid hamartoma (REAH). Int Forum Allergy Rhinol., 2013 Mar 3;3(3):248–253.
7. Ozolek J.A., Hunt J.L. - Tumor suppressor gene alterations in respiratory epithelial adenomatoid hamartoma (REAH): Comparison to sinonasal adenocarcinoma and inflamed sinonasal mucosa. Am J Surg Pathol., 2006;30:1576–1580.
8. Roffman E., Baredes S., Mirani N. - Respiratory epithelial adenomatoid hamartomas and chondroosseous respiratory epithelial hamartomas of the sinonasal tract: A case series and literature review. Am J Rhinol., 2006;20:586–590.
9. Avilés Jurado F.X., Guilemany Toste J.M., Alobid I., Alós L., Mullol i Miret J. - The Importance of the Differential Diagnosis in Rhinology: Respiratory Epithelial Adenomatoid Hamartoma of the Sinonasal Tract. Acta Otorrinolaringol Esp., 2012;63(1):55-61.
10. Gajda M., Zagolski O., Jasztal A., Lis G.J., Pyka-Fosciak G., Litwin J.A. - Respiratory epithelial adenomatoid hamartoma of the anterior nasal septum a rare localisation of an unusual tumour in a child: a case report. Cases J., 2009;2:8151.
11. Athre R., Ducic Y. - Frontal Sinus Hamartomas. Am J Otolaryngol., 2005;26(6):419-421.
12. Himi Y., Yoshizaki T., Sato K., et al. - Respiratory epithelial adenomatoid hamartoma of the maxillary sinus. J Laryngol Otol., 2002;116:317-318.
13. Endo R., Matsuda H., Takahashi M., Hara M., Inaba H., Tsukuda M. - Respiratory Epithelial Adenomatoid Hamartoma in the Nasal Cavity. Acta Oto-laryngologica., 2002;122(4):398-400.
14. Delbrouck C., Fernandez Aguilar S., Choufani G., Hassid S. - Respiratory epithelial adenomatoid hamartoma associated with nasal polyposis. American Journal of Otolaryngology - Head and Neck Medicine and Surgery, 2004 July;25(4):282-284.
15. Marin L.G., Trombitas V., Albu S. - A case of respiratory epithelial adenomatoid hamartoma. Chirurgia, 2013;108(6):904-906.
16. Cao Z., Gu Z., Yang J., Jin M. - Respiratory epithelial adenomatoid hamartoma of bilateral olfactory clefts associated with nasal polyposis: Three cases report and literature review. Auris Nasus Larynx., 2010 June;37(3):352-356.
17. Seol J.G., Livolsi V.A., O'Malley B.W., Chen J.Y., Loevner L.A. - Respiratory Epithelial Adenomatoid Hamartoma of the Bilateral Olfactory Recesses: A Neoplastic Mimic? American Journal of Neruroradiology, 2010 Feb;31(2):277-279.
18. Hawley K.A., Ahmed M., Sindwani R. - CT Findings of Sinonasal Respiratory Epithelial Adenomatoid Hamartoma: A Closer Look at the Olfactory Clefts. American Journal of Neuroradiology, 2013;34:1086-1090.
19. Weinreb I. - Low Grade Glandular Lesions of the Sinonasal Tract: A Focused Review. Head Neck Pathol., 2010 Mar;4(1):77-83.
20. Fitzugh V.A., Mirani N. - Respiratory Epithelial Adenomatoid Hamartoma: A Review. Head neck Pathol., 2008;2(3):203-208.
21. Flavin R., Russel J., Phelan E., McDermott M.B. - Chondro-osseous respiratory epithelial adenomatoid hamartoma: a case report. International Journal of Pediatric Otorhinolaryngology, 2005 Jan;69(1):87-91.
22. Ozolek J.A., Barnes L.E., Hunt J.L. - 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., 2007 Apr;131(4):530-537.
23. Perez-Ordonez B. - Hamartomas, papillomas and adenocarcinomas of the sinonasal tract and nasopharynx. J Clin Pathol., 2009;62(12):1085-1095.