Update on Inverted Epithelial Lesions of the Sinonasal and Nasopharyngeal Regions

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Introduction

The nasal inflammatory or allergic polyps (NP), inverted and fungiform papillomas have been recognized for a considerable time. Recently respiratory epithelial adenomatoid hamartoma (REAH) has attracted attention, but some features of this lesion are still obscure.

The invagination of the embryonic olfactory ectoderm gives rise to the Schneiderian membrane that ultimately forms the respiratory mucosal lining of the nasal cavity and paranasal sinuses and is consisting of pseudostratified columnar ciliated epithelium with interspersed goblet cells [1]. Like the embryonic developmental pattern of the ectoderm, invagination or inversion of the surface epithelium is a feature of this mucosa, which is also identified in nasopharyngeal and sinonasal lesions; NP, REAH and IP (Figs. 1–4).

Inverted Papillomas

The inverted papillomas (IP) most commonly originate from the mucosa of the lateral nasal wall and paranasal sinuses but orbital, anterior skull base and even temporal bone cases have been described and they may be multicentric.

IP are relatively rare comprising 0.4–7% of sinonasal tumors, while in our series it was 12.1% [1, 26]. The rate of

malignant transformation was 11% in a collective review of 1390 cases [1].

Inverted papillomas are recognized by their characteristic feature of inversion of the epithelium into the underlying stroma. The epithelium may be respiratory, transitional or squamous surrounded by a basement membrane, containing mucin filled microcysts underlying the surface epithelium [20]. The morphology led to the classification of these cases as mucinous and Schneiderian or mixed [2]. Michaels and Young [23] evaluated the papillomas of the nose and paranasal sinuses and described IP cases as severe squamous metaplasia of the surface epithelium and duct epithelium like Oberman et al. many years ago. And they stated that, they agreed with Oberman's suggestion that IP is the result of the metaplasia of the pre-existing ducts which lost their seromucus glands as it is frequently observed in nasal polyps and thus the first step of the progression of IP might be similar to an inflammatory polyp. Shortly there are two hypothesis for the origin, metaplastic inversion of the surface epithelium or metaplasia of surface and ductal epithelium.

Patterns of Cytokeratin Expression

Hicks W Jr et al. [12] and Schwerer MJ et al. [28] evaluated the expression patterns of cytokeratins in nasal polyps and IP. The columnar differentiation cytokeratins (ex: CK 7,8,18,19,20) were positive in both NPs and IPs but the squamous differentiation cytokeratins (ex: CK 10,10/13, 1/2/10/11) were positive in IP but not in NP. For both group of cases the immature cell type CKs were positive at the basal layer. On the other hand the CK expression patterns of REAH is not evaluated.

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Fig. 1 Respiratory epithelial adenomatoid hamartoma like regions in a nasopharyngeal biopsy (H&E, original magnification $\times 10$)

Fig. 4 Inverted papilloma with squamous metaplasia but not dysplasia (H&E, original magnification $\times 10$)

Fig. 2 Nasal polyp with inverted proliferation of the surface epithelium (H&E, original magnification $\times 10$)

Fig. 3 Respiratory epithelial adenomatoid hamartoma of the nasal cavity (H&E, original magnification $\times 10$)

Dysplasia

IP are generally accepted as neoplastic, but although the metaplastic epithelium may exhibit dysplasia there are uncertainties about its nature. Califano et al. [3] analyzed the pattern of X chromosome inactivation in IPs from four female patients and all four lesions demonstrated a monoclonal pattern of inactivation. Inactivation of a single allele is a feature of monoclonal proliferations and may be indicative of a neoplastic process. Also in this series, loss of heterozygosity (LOH) on chromosomal arms 3p, 9p21, 11q13, 13q11, and 17p13 were analysed. These are the regions where frequently losses occur during neoplastic transformation of the upper respiratory tract epithelium. LOH was not detected in any non-dysplastic areas from the 28 IP and they concluded that IPs are monoclonal proliferations, yet they do not fit the profile of a prototypic precursor lesion of the upper respiratory tract, unlike squamous epithelial dysplasia. It is well known that IP is not always associated with dysplasia, and keeping in mind their progression may be unlike squamous dysplasia depending upon the observations of Califano et al. we are in need of prognosis related histopathological features of dysplasia for IP. Katori et al. [15] used the following microscopic changes seen within IP to establish the diagnosis of dysplasia, which are not constantly used: slight dysplasia—little or no hyperplasia with hyperkeratosis in the cell of the basal layer of IP; moderate dysplasia—irregular stratification, mitosis and loss of polarity in the cell of the basal and suprabasal layer of IP; and severe dysplasia—individual cell keratinization, increased mitosis in surface, occasional atypical mitosis, and dysplasia changes in all of the layer. They identified increased MMP-2 and 9 expressions in IP with dysplasia and carcinoma. Kaufman et al. [18] reported dysplasia in 67.6% of IP and divided the cases in two groups as mild and focal

moderate and diffusely moderate to severe but did not describe the applied criteria.

Fan GK et al. [7] evaluated a series of IP and IP with carcinoma and among 32 cases of IP they identified dysplasia in 9 (28%) cases. The incidence of dysplasia in different series may be related to different criteria applied. As might be expected Ki67 was higher in IP with dysplasia. p53 overexpression was directly correlated with the Ki67 index in IP and primary SCC diseases. Schwerer et al. [29] described a tendency toward increasing p53 protein expression from non-papillomatous nasal mucosa to inverted papilloma, as well as along the metaplastic process from columnar (respiratory) to transitional (cuboidal) and finally squamous epithelium within inverted papillomas. When only dysplastic IP were included, they identified increased cell proliferation along with the development of dysplasia and carcinoma in situ which was associated with reduced p27Kip1 expression. There are no published cases of dysplasia in REAH.

Association with Viruses

Smoking and viral infections are among the suspects of IP development. HPV is evaluated both for IP and nasal polyps but not for REAH [9, 13, 19]. Kraft et al. [19] identified HPV11 in only 1(3%) out of 29 IP cases, while HPV 6b, 16 and 18 were negative by in situ hybridization. Hoffman M et al. [13] detected HPV DNA type 6 and 11 in 3 of 26 cases, while 20 nasal polyps were negative. In an earlier article they had reported one positive case among 31 nasal polyps. There are articles which detected HPV-DNA in higher frequency in nasal polyps probably related to problems with methodology.

McKay SP et al. [22] described HPV transcripts were present in SCC positive for HPV, and the relative level of E7 to E5 transcripts indicated integration of the viral genome. These findings are suggestive of HPV having an active role in the lesion.

Macdonald MR et al. [21] reported EBV DNA in 13 (65%) cases among 20 IP, while ten nasal polyps were negative. Also they identified HPV6/11 in 8 cases and HPV16 in one case. Five cases were both HPV and EBV positive. On the other hand Gaffey et al. [10] reported a much lower incidence of EBV DNA in IP, only one among 12 cases along with a positive case of squamous cell carcinoma arising from an IP and suggested that higher incidences might be related to the EBV positive lymphocytes infiltrating the IP areas. We don't know the HPV and EBV incidence in REAH.

Prognostic Histological Factors

Eggers G et al. [5] evaluated histological parameters that might be of prognostic value in a series of 93 IP cases with recurrences of 13 cases and malignant transformation in 12. They did not find any significant difference when type of epithelium (squamous, transitional, cylindrical), the number of cell layers, the stroma-epithelium ratio, the content of fibres, eosinophilia, and inflammation when these groups were considered, but they identified increased mitosis and dyskeratosis as risk factors. In a series of 19 IP cases Katori et al. [17] reported malignancy was related to the presence of bone invasion, the absence of inflammatory polyp, increase in the ratio neoplastic epithelium:stroma, increase in hyperkeratosis, the presence of squamous epithelial hyperplasia, increase in the mitotic index and a decrease in the number of eosinophils. Multiple recurrences (without malignancy) were related to frontal sinus origin, increase in hyperkeratosis, the presence of squamous epithelial hyperplasia and increase in the mitotic index. Clinically benign behaviour was related to the presence of inflammatory polyp and the absence of hyperkeratosis.

REAH

REAH is described as a non-neoplastic lesion arising from the mucosal epithelium and seromucus glands of the sinonasal region, nasal septum, nasopharynx as well as ethmoid and frontal sinuses. On the other hand in 2006 Ozolek et al. [24] identified LOH in REAH with patterns resembling sinonasal adenocarcinomas and suggested that these lesions might be neoplastic. The microscopic features of REAH are well developed, branching glands frequently in direct continuity with the surface epithelium and composed chiefly of ciliated respiratory epithelium, which may be cuboidal or flat, surrounded by a thick basement membrane [4, 6, 11, 27, 30]. Some hamartomas with osseochondroid components are described [8, 14].

A large majority (70%) of the REAH was described at the nasal cavity and 80% of the cases are males, age of the patients ranging from 30 to 90 [4, 6, 11, 30]. The REAH, originating from the surface epithelium and seromucus glands, arise at an inflammatory background. Glands, lined by a ciliated respiratory epithelium proliferate into the submucosa. The epithelial lining of the glands may be cuboidal, flattened or mucous glandular and squamous metaplasia may be expected. Stromal hyalinization and luminal mucinous material accumulation are frequently identified, but a complex glandular pattern is unlikely.

Differential Diagnosis

The differential diagnosis of REAH includes IP, teratoma, inflammatory polyps and adenocarcinomas and IP should be differentiated from squamous cell carcinoma and REAH [4, 6, 11, 14, 16, 30].

The differential diagnosis of REAH and polyps is confusing in cases when the adenomatoid proliferation is not florid. It is suggested that the notable clinical difference is involvement of the nasal septal area (particularly the posterior portion) in REAH. REAH may be more indurated. Histologically, they have similar features but more adenomatoid proliferation, abundant basement membrane material and atrophic epithelial changes are in favor of REAH.

For the differential diagnosis with IP, epithelial marked thickening with mucocytes, intraepithelial mucous cysts, and inflammatory cells favor IP. REAH can be distinguished by its adenomatoid structures lined by epithelium not exceedingly thick, often composed of a single layer [27]. REAH occurs primarily on the posterior nasal septum while IP occurs mainly at the lateral nasal wall and sinuses.

Even in 2006, we came up with articles questioning if nasal polyps and inverted papilloma (IP) have similar disorders in cell cycle regulation [25]. The association of IP with nasal polyps is not infrequent; more than 20% of IP may show association. “Squamous metaplasia” seems like a constant feature for IP. The morphological features are overlapping in some cases. Association of nasal polyps and REAH is also expected. For example, the case presented by Delbrouch et al. [4] is a REAH occurring in a nasal polyp and the differential diagnosis is difficult depending on the microphotographs. REAH is described as “occasional invaginations of the surface lining of the ciliated respiratory epithelium that continued directly to the submucosal glands. Invaginations of the surface epithelium of the nasal polyps are a very common feature and continuity with the submucosal glands is not a prerequisite for REAH, it is hard to define the limits of this diagnosis.

When a new entity is proposed it's a good idea to evaluate the archives and see if similar lesions existed, what were the diagnosis and the outcome? When we look back, we met diagnosis of IP and NP in our archives for possibly cases with REAH. And it would have been probably “adenocarcinoma” for the mucinous variant of the REAH.

We re-evaluated 26 nasal lesions with inverted growth pattern and tried to classify the cases into three categories:

- 1 *Cases with only features of IP:* Predominantly inverted proliferations composed of dilated duct like structures, lined by multiple layers of squamous, ciliated, columnar or transitional epithelium.
- 2 *Cases with only features of a REAH:* Characterized by well developed, increased, branching glands frequently in direct continuity with the surface epithelium and composed of chiefly ciliated respiratory epithelium, but may be cuboidal or flat with or without mucous gland metaplasia (Fig. 5).
- 3 *Cases with IP and REAH:* Any patient with histopathological features of both IP and REAH in any of his/her biopsies (recurrent or not) (Figs. 6–8).

In our series of 38 operation specimens from 26 cases, 73.1% of the cases were IP, 4 were REAH and 3 had features of both IP and REAH. Without well established criteria it was hard to determine the incidence of dysplasia but there were some demonstrative cases (Fig. 9). One pure IP case was associated with in situ carcinoma (Fig. 10) and another was associated with an invasive carcinoma.

Fig. 5 Respiratory epithelial adenomatoid hamartoma with mucous gland metaplasia of the nasal cavity (H&E, original magnification $\times 20$)

Fig. 6 Respiratory epithelial adenomatoid hamartoma like areas of inverted papilloma (H&E, original magnification $\times 20$)

Fig. 7 Respiratory epithelial adenomatoid hamartoma like areas of inverted papilloma (H&E, original magnification $\times 20$)

Fig. 8 Respiratory epithelial adenomatoid hamartoma like areas of inverted papilloma (H&E, original magnification $\times 20$)

Fig. 9 Low grade dysplasia in an inverted papilloma (H&E, original magnification $\times 40$)

This close approximation of IP and REAH areas in many cases with overlapping morphological features might raise the questions about terminology; previously one was

Fig. 10 Carcinoma in situ in IP (H&E, original magnification $\times 20$)

accepted as a “neoplasm”, while the other a “hamartoma”, but recently both were figured out to be probably neoplastic [3, 24]. Furthermore, there are many microscopic fields in especially nasal polyps and nasopharyngeal biopsies that may resemble REAH very closely, however only identified in smaller areas.

The hamartoma term might be reserved smoothly for cases with chondro-osseous and epithelial components. Pure epithelial lesions require further evaluation in order to provide strict differential diagnostic features between pure or predominantly respiratory cell IP and nasal polyps with extensive surface mucosal invaginations.

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