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Respiratory Epithelial Adenomatoid Hamartoma is Frequent in Olfactory Cleft After Nasalization

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Objectives: To assess the site and histopathology of polyps at the first revision surgery for recurrent nasal polyposis (NP) after radical ethmoidectomy (nasalization).

Study Design: Retrospective study.

Methods: Between January 2008 and December 2015, a total of 62 patients having undergone revision surgery for recurrent NP after nasalization were included. The site and histology of the recurrence of polyps were analyzed according to operative and pathological reports.

Results: Histology showed classical inflammatory nasal polyps (CINP) in 91% of nasal cavities at primary surgery versus respiratory epithelial adenomatoid hamartoma (REAH) or REAH associated to CINP in 54.8% at revision surgery ($P < .0001$). Polyps were principally observed in the ethmoidal complex in 70% of nasal cavities during primary surgery and in the olfactory clefts in 88.7% during revision surgery ($P < .0001$). The mean interval between nasalization and first revision surgery was 8.8 ± 4.4 years (0.4–21.7 years). This interval was significantly shorter for grade 3 polyps, polyps removed from both ethmoidal complex and olfactory cleft at primary surgery, association of CINP and REAH at primary surgery, and when primary surgery had preserved the middle turbinates.

Conclusion: Polyp recurrences after nasalization were mainly observed in the olfactory clefts and can be different histological features: inflammatory polyps, respiratory epithelial adenomatoid hamartoma, or a combination of both.

Key Words: Recurrent nasal polyposis, respiratory epithelium adenomatoid hamartoma, olfactory cleft, nasalization, ethmoid.

Level of Evidence: 4

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INTRODUCTION

Nasal polyposis (NP), a condition with an approximated prevalence of 2.1% in the French population,[1] is a chronic inflammatory disease of the ethmoid. Diagnosis of NP is based on nasal endoscopy with the presence of bilateral nasal edematous polyps. Endoscopic sinus surgery has been shown to improve symptoms of NP when the disease becomes uncontrolled with medical treatment. However, revision surgeries are often required because of high recurrence.

At primary surgery, classical inflammatory nasal polyps (CINP) are frequently observed within different subcompartments of the ethmoid bone, especially in the ethmoidal complex (EC) from which polyps protrude through the middle or superior meatus.[2] To the best of our knowledge, the site of recurrence of NP was reported in only one paper of Bassiouni et al.[3] The authors found recurrent polyps stemming mostly from the frontal sinus area (55%) or the EC (37%) during revision surgeries. However, according to our experiences, recurrent polyps stem frequently from the olfactory recess which is the upper portion of the olfactory cleft (OC).[4] Respiratory epithelial adenomatoid hamartomas (REAH) and CINP can be observed in revision surgery after radical ethmoidectomy (nasalization), and REAH was apparently more frequently found in the olfactory cleft.[5,6] Thus, the aim of our study was to compare the compartment of origin and histopathology of polyps found in primary and revision surgery for NP.

MATERIAL AND METHODS

Patients

Only patients with symptomatic recurrent nasal polyps after a previous radical ethmoidectomy, who underwent a first revision surgery between January 2008 and December 2015, were enrolled in this retrospective study. A total of 62 consecutive patients who had first and revision surgeries performed by the same surgeon (R.J.) in our tertiary university hospital were included. Revision surgery explored

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individually on each side of the EC and olfactory cleft left by the previous surgery. Data were found in patients' medical records and collected from operative and pathological reports of the primary surgery (nasalization) and the revision surgery.

All patients were operated under endoscopic control according to a radical ethmoidectomy procedure called nasalization, described below. Patients were operated when medical treatment failed to control the nasal symptoms, either for primary or revision surgeries. No systemic corticosteroid or antibiotic treatment was given neither before nor after surgery. Patients began nasal saline irrigations and topical steroid sprays the day after surgery. A long-term topical steroid treatment was recommended for all patients.

Patients under 18 years old, or those suffering from cystic fibrosis, primary mucociliary dyskinesia syndrome (Kartagener syndrome), Mounier Kuhn syndrome, Churg-Strauss syndrome, or other chronic edemato-purulent rhinosinusitis without polyps were excluded. This study was approved by the Institutional Review Board of University Hospital of Nancy, France.

Surgical Procedure

Nasalization (also written nasalisation) is a surgical technique designed to remove as completely as possible the non-olfactory mucosa of the EC. The surgical technique of nasalization, as described in 1995[7,8] was performed as follows. Middle antrostomy was performed to allow a safe dissection and removal of the mucosa on the orbital wall of the EC. Frontotomy (dissection of the anterior EC to free the frontal ostium) and sphenoidotomy (key to identify the roof of the EC) were associated to middle turbinate resection to finely dissect and remove as completely as possible the mucosa inside the EC and both on the ethmoid roof and the conchal lamina lateral aspects. The conchal lamina is a thin plate of bone which was preserved at the upper part of the turbinate wall of the EC.[9] It anatomically protects the olfactory recess in which most of the olfactory mucosa is located. The middle turbinate was preserved in some patients if it was considered non-affected by the disease. The OC was systematically explored during the surgical procedure and polyps inside the OC were removed if they were observed. The endoscopic surgery of the olfactory cleft was performed with sparing as much of the sensory mucosa as possible. As the sensory mucosa cannot be identified endoscopically, resection must be a compromise between resection of CINP/REAH and preservation of olfactory cleft mucosa with a healthy appearance. The resection technique consisted of resection of diseased mucosa (CINP/REAH) preserving the underlying periosteum, and was based on endoscopic punch resection (Blakesley nasal forceps) of the diffuse polypoid pathological mucosa (or the implantation base of the pedunculated polyp). The periosteum/perichondrium can and must be spared to avoid septal perforation in bilateral forms.[10]

Revision surgery after nasalization started by identifying the conchal lamina. Recurrent polyps were endoscopically followed to their pedicle before being removed with Blakesley forceps at their origin, which was located either lateral (EC compartment) or medial to the conchal lamina (OC compartment). Complete dissection and removal of the diseased mucosa inside the previous exenterated EC was then performed only when recurrence was originating from EC. Removal of the diseased mucosa in the OC was performed with different-angled and non-cutting Blakesley forceps; it consisted of resection of CINP/REAH preserving the olfactory cleft mucosa with a healthy appearance and the underlying periosteum on both parasagittal walls (nasal septum and conchal lamina) of the OC while carefully preserving the cribriform plate mucosa.[10] The status of the OC was assessed and noted in the operative report.

Histopathology (figure 1A-D)

All surgical specimens removed from the OC compartment and the EC compartment were separately sent for pathological processing. The pathological diagnosis of REAH was based on Wenig and Heffner's criteria.[11] Lesions were considered as REAH in case of "presence of fragments ≥ 5 mm, made of pseudoglands lined by ciliated respiratory epithelium separated by thin bands of intervening stroma with a width lesser or equal to the average mean diameter of glands."[12] Inflammatory polyps were characterized by polyp tissue with frequent epithelial damage, a thickened basement membrane, and stroma in which the interstitium was composed mainly of edematous connective tissue and consists of supporting fibroblasts and infiltrating inflammatory cells.[13,14]

Data Collection

Data were collected from medical records regarding demographic, operative, and histopathological records (primary and revision surgery) as follow: age, gender, asthma status (yes/no), aspirin intolerance status (yes/no), date of surgery, staging of polyps (according to Mackay and Nacleiro's classification[15]), site of origin of polyps (EC, OC, or both), middle turbinate status (removed/preserved), and histopathological feature of polyps (CINP or REAH).

Statistical Analysis

Descriptive statistics for quantitative variables were expressed as mean ± standard deviation (SD) and for qualitative variables as percentages. All data were examined for normality using Shapiro-Wilk's tests. Chi-squared or, when necessary, Fisher's exact tests were used for categorical variables. For continuous variables, the Wilcoxon-Mann-Whitney test was used for the comparison of two groups and the Kruskal-Wallis test for the comparison of three groups because of the non-normal distribution of samples. Analyses were conducted using SAS v9.1 statistical software (SAS Inst., Cary, NC). A two-tailed value of $P < .05$ was considered statistically significant.

RESULTS

A total of 62 patients (27 women and 35 men; mean age, 44.9 ± 12.1 years; age range, 22.1–72.7 years) undergoing revision surgery for recurrent NP after primary nasalization were included. Fifteen patients were asthmatic (24%), and 24 patients (38.7%) were asthmatic with

TABLE I.
Polyps' Characteristics at Primary and Revision Surgery.

	Primary Surgery	Revision Surgery	*P*
Polyp staging*	n = 107 (missing data = 17)	n = 100 (missing data = 24)	
1	40 (37.4%)	48 (48%)	.3
2	58 (54.2%)	45 (45%)	
3	9 (8.4%)	7 (7%)	
Histopathological feature	n = 124	n = 124	
CINP	113 (91.1%)	56 (45.2%)	<.0001
REAH	0	21 (16.9%)	
CINP+REAH	11 (8.9%)	47 (37.9%)	
Site of polyp origin	n = 120 (missing data = 4)	n = 124	
EC	84(70%)	14 (11.3%)	<.0001
OC	7 (5.8%)	51 (41.1%)	
Both EC + OC	29 (24.2%)	59 (47.6%)	

*According to Mackay and Nacleiro's classification. CINP = classical inflammatory nasal polyp; EC = ethmoidal complex; REAH = respiratory epithelial adenomatoid hamartoma; OC = olfactory cleft.

aspirin intolerance (Widal's triad). Hence, data from 124 nasal cavities were analyzed. Middle turbinates were removed at primary surgery in 111 cavities (89.5%) and preserved in 13 cavities (10.5%).

Table I shows the polyp characteristics at primary and revision surgery. Polyp histopathological characteristic was exclusively inflammatory (CINP) in 91% of nasal cavities at primary surgery whereas REAH or REAH associated to CINP were observed in 54.8% of nasal cavities at revision surgery ($P < .0001$). Polyps originated exclusively within the EC in 70% of nasal cavities at primary surgery, and in only 11.3% of nasal cavities at revision surgery ($P < .0001$). Inversely, recurrent polyps originated mainly in the OC after nasalization: exclusively within the OC in 41.1% and both in OC and EC in 47.6% of nasal cavities.

Table II shows polyp histopathological features according to the sites of polyp recurrence at revision surgery. There was a significant difference between the histopathological types of recurrent polyps in different sub-compartments of the ethmoid ($P < .0001$). In 14 nasal cavities in which polyps recurred exclusively within the EC, histopathological analysis showed CINP in 12 nasal cavities. In 51 nasal cavities in which recurrent polyps were exclusively observed in the OC, histopathology revealed CINP in 21 nasal cavities, REAH in 17, and both CINP and REAH in 13. In 59 nasal cavities in which recurrent polyps were observed in both EC and OC, CINP was found in 23, an association of CINP and REAH in 33, and isolated REAH in three nasal cavities.

TABLE II.
Distribution of Polyp Histopathology According to the Sites of Recurrence of Polyps.*

	Site of polyp recurrence		
Polyp histopathology	EC	OC	EC + OC
CINP	12	21	23
REAH	1	17	3
CINP + REAH	1	13	33

*$P < .0001$.
CINP = classical inflammatory nasal polyp; EC = ethmoidal complex; REAH = respiratory epithelial adenomatoid hamartoma; OC = olfactory cleft.

TABLE III.
Time Interval Between Primary and Revision Surgery According to Clinical Characteristics at First Surgery.

	Time Interval ± SD [range] (years)	*P*
Gender		
Male (N = 35)	9.2 ± 4.4 [0.6–17.0]	.15
Female (N = 27)	8.3 ± 4.4 [0.4–21.7]	
Middle turbinates status at first surgery		
Removed (n = 111)	9.5 ± 4.2 [0.6–21.7]	<.0001
Preserved (n = 13)	3.4 ± 1.7 [0.4–5.5]	
Widal's triad		
Yes (n = 48)	8.7 ± 3.3 [3.6–14.6]	.94
No (n = 76)	8.9 ± 5.0 [0.4–21.7]	
Polyp staging*		
1 (n = 40)	9.2 ± 4.6 [0.4–17]	.012
2 (n = 58)	8.2 ± 3.8 [0.6–16.4]	
3 (n = 9)	4.8 ± 1.9 [2.1–7.0]	
Site of polyp origin		
EC (n = 84)	9.0 ± 4.0 [0.4–17.0]	.009
OC (n = 7)	8.8 ± 2.0 [4.8–11.7]	
Both (n = 29)	6.9 ± 4.1 [2.1–17.0]	
Histopathological feature		
CINP (n = 113)	9.1 ± 4.5 [0.4–21.7]	.0066
CINP + REAH (n = 11)	5.6 ± 1.4 [2.8–7.6]	

*According to Mackay and Nacleiro's classification. CINP = classical inflammatory nasal polyp; EC = ethmoidal complex; REAH = respiratory epithelial adenomatoid hamartoma; OC = olfactory cleft.
N = number of patients; n = number of nasal cavities.

The mean time interval between primary and first revision surgery was 8.8 ± 4.4 years (means, 8.8 years; range, 0.4–21.7 years). Table III shows the interval between primary and revision surgery according to clinical characteristics at primary surgery. This interval was significantly shorter for the following characteristics at primary surgery: middle turbinate sparing ($P < .0001$), grade 3 polyps ($P = .012$), presence of polyps in both EC and OC ($P = .009$), or when CINP and REAH were associated ($P = .0066$). Gender and Widal's triad did not impact significantly on the mean interval between primary and first revision surgery.

DISCUSSION

The findings of the present study can be summarized as follows: i) the olfactory cleft is a frequent site of NP recurrence after radical ethmoidectomy (nasalization); ii) 54.8% of recurrent polyps are REAH or REAH associated to CINP; iii) the mean interval between primary radical surgery with middle turbinate resection and the first revision surgery is 9.5 years; and iv) middle turbinate sparing, grade 3 polyps, polyps initially extended both in the EC and the olfactory cleft, and the

association between REAH and CINP at primary surgery were predictive factors for an earlier revision surgery.

Until now, the pathophysiology of NP is still a matter of debate. Most expert panel documents are based on the assumption that rhinitis and sinusitis are concurrent in most individuals,[13] so as the current concept recognizes NP as a form of chronic rhinosinusitis (CRS).[13] However, based on endoscopic observations,[2] CT-imaging and the evo-devo origin of the human ethmoid complex,[4,16] NP may also be regarded as a specific disease of the ethmoid complex. In fact, the origin and development of the ethmoid bone and paranasal sinuses (ie, the maxillary, frontal, and sphenoid sinuses) are quite different[4] and each of these organs may be at risk of specific diseases. The ethmoid is the bony receptacle of the olfactory mucosa in the anterior skull base in all vertebrates,[16] but because of bipedal acquisition, the specific human ethmoid complex is anatomically compartmentalized into a EC and an olfactory cleft in each nasal fossa.[4] In NP, edematous polyps develop from the nonolfactory mucosa of the EC and protrude into the nasal fossa through the middle meatus and in the olfactory cleft through the superior and supreme meati and sphenoethmoidal recess.[2] Pathological features of polyps that develop from the mucosa of the OC can be either classic edematous polyps (CINP) or REAH. Our hypothesis is that NP develop from the nonolfactory mucosa found in the EC, which could be vestigial olfactory mucosa having lost its histological and functional features and could trigger some immune pathway to produce self-targeting reaction. Recent papers actually support our hypothesis of an autoimmune disease. De Schryver et al.[17] found evidence of autoimmunity in patients with nasal polyps. They have brought out that anti-dsDNA IgG and IgA were at increased levels in nasal polyps while they

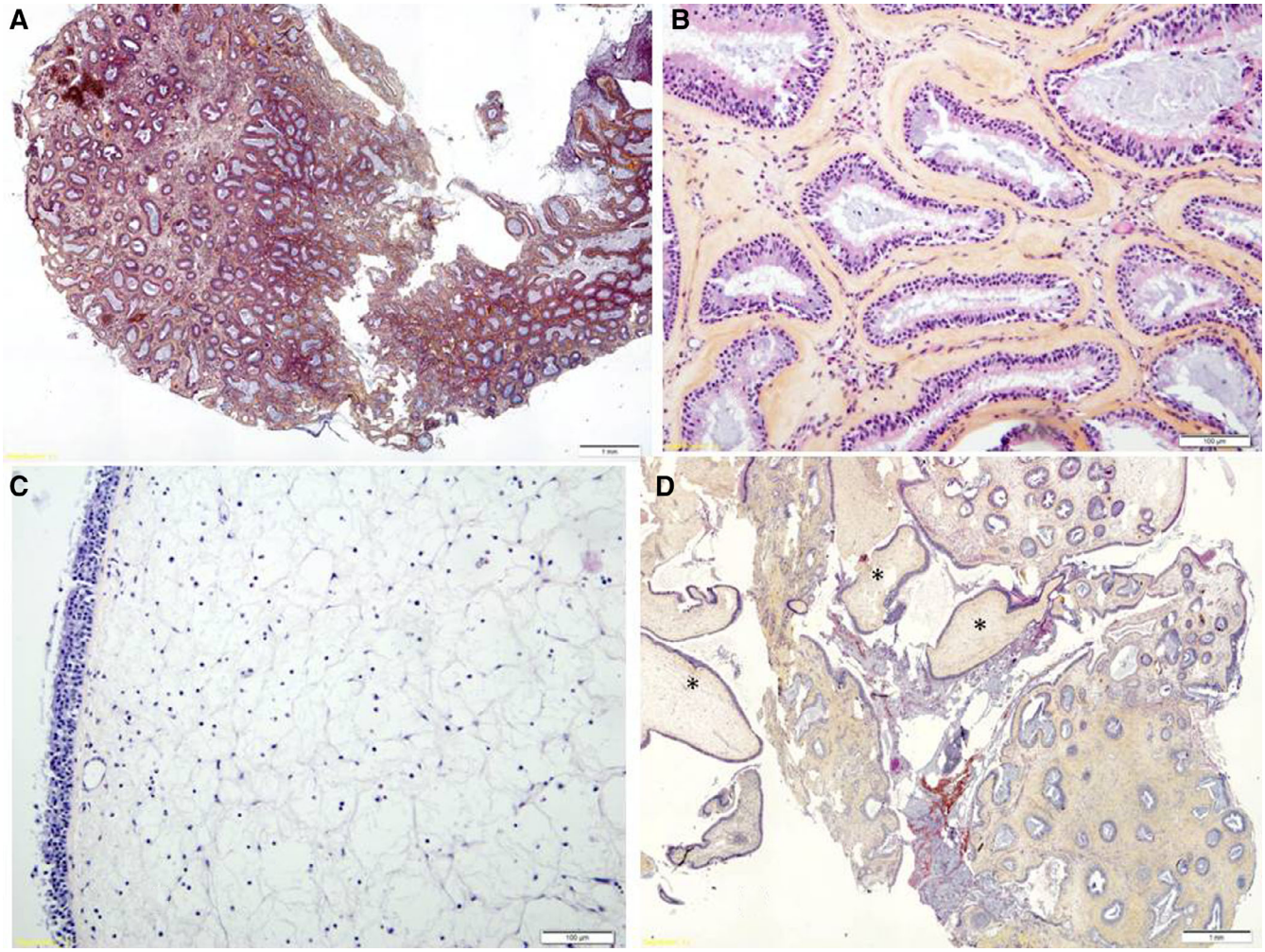

Fig. 1. Histopathological features of REAH (A–B), classical inflammatory nasal polyps (C), and mixed patterns (D). A–B: REAH is characterized by submucosal adenomatoid proliferation taking origin from surface epithelium (A). These widely spaced, small to medium-sized pseudoglands, which invaginate downward into the submucosa and are separated by stroma tissue, arise in direct continuity at the surface of the epithelium (B). CINP is characterized by edema, goblet cell hyperplasia of the epithelium, thickening of the basement membrane, and of numerous leukocytes, predominantly eosinophils. Mixed patterns are characterized by presence of submucosal adenomatoid proliferation invaginating downward into the submucosa of REAH and edema, goblet cell hyperplasia of the epithelium with thickening of the basement membrane of CINP (asterisks). CINP = classical inflammatory nasal polyp; REAH = respiratory epithelial adenomatoid hamartoma.

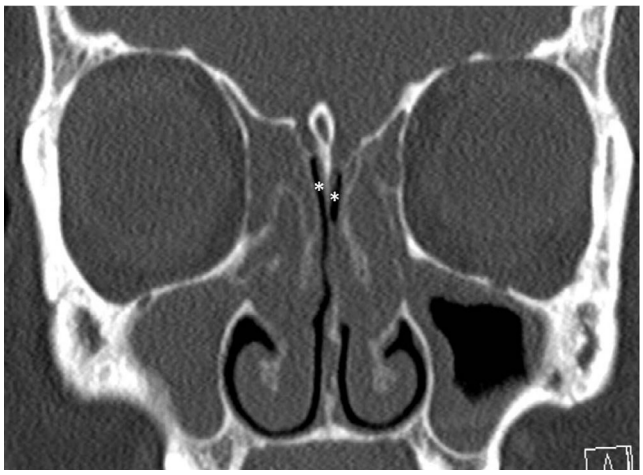

Fig. 2. Coronal computed tomography scan of a patient with nasal polyps without previous sinus surgery: polyps are principally observed inside the ethmoidal complex. The olfactory clefts (white asterisks) are free of polyps and were not widened.

were not significantly elevated in serum samples. Based on this concept, our aim of surgery in NP is to remove as much as possible the non-olfactory ethmoidal mucosa because the residual non-olfactory mucosa could be a potential trigger for polyp recurrence.

Our findings show that polyps developed mainly inside the EC (70% of nasal cavities) (Fig. 2) and were inflammatory at primary surgery. After radical ethmoidectomy, the recurrent disease has a tendency to develop medially toward the olfactory cleft (Fig. 3A–D). Moreover, the pathological feature is likewise different from the one before surgery. REAH was observed in more than a half of nasal cavities in patients with polyp recurrence after radical ethmoidectomy. We suggest that at onset of the disease, there is an importantly inflammatory phenomenon occurring in the non-olfactory mucosa inside the EC. This inflammatory phenomenon could be aimed to destroy the trigger structures in the vestigial epithelium of the EC. This phenomenon is probably less important within the OC in which the olfactory mucosa has been restricted by evolution and in which there is less vestigial, nonolfactory mucosa. This could explain the absence of polyps inside the OC in the majority of case at primary surgery. As radical ethmoidectomy is a surgical technique designed to remove as completely as possible the nonolfactory mucosa of the EC, the recurrence should therefore mostly occur within the OC. Interestingly only 14/124 of the EC were the site of

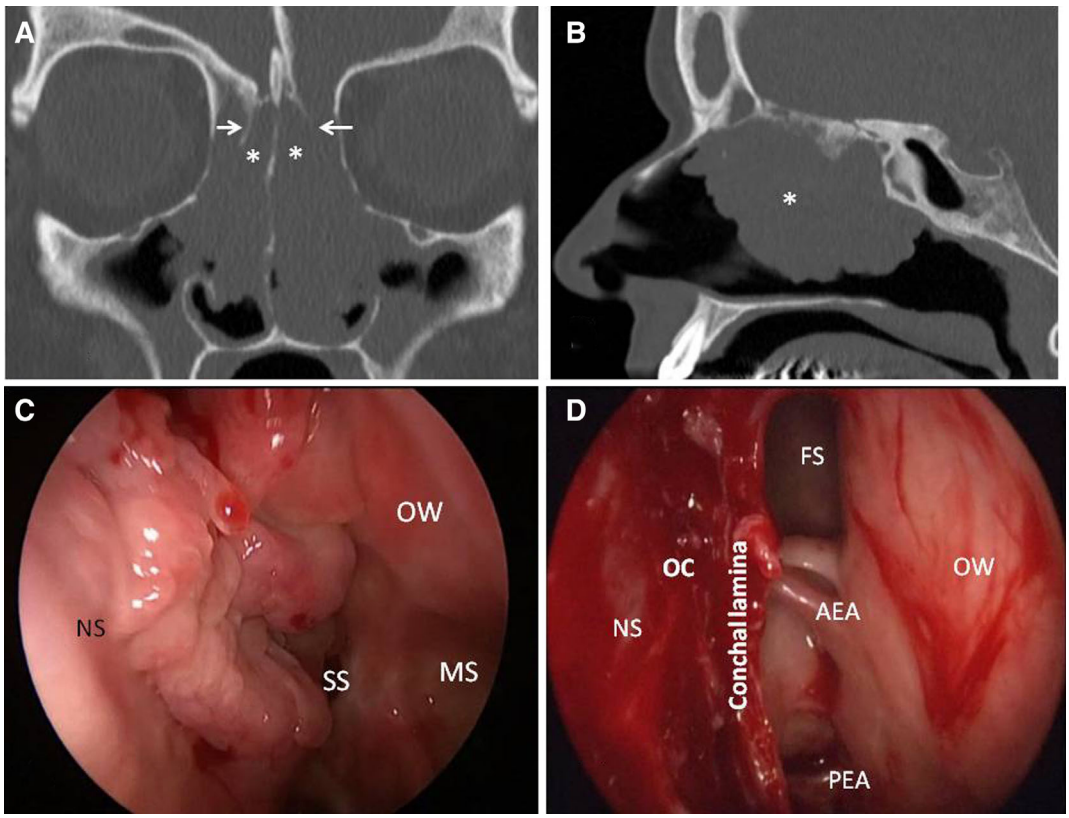

Fig. 3. Patient with history of nasalization with middle turbinate resection and large opening of all paranasal sinuses 17 years ago. The first revision surgery was performed 17 years after nasalization. (A) Coronal CT scan before revision surgery showed voluminous polyps developing essentially inside the olfactory clefts (white asterisks) which were widened and pushed laterally the conchal lamina (white arrows); (B) Sagittal CT scan of the left nasal cavity showed voluminous polyps stemming from the olfactory cleft; (C) Per-operative endoscopic aspect of the left nasal cavity of this patient at revision surgery: huge polyps stemming from the left olfactory cleft; (D) Endoscopic aspect of the left nasal cavity after removal of polyps: polyps were observed only inside the olfactory cleft, the mucosa of left ethmoidal complex was free of polyp recurrence. Pathological results confirmed a huge REAH with some small inflammatory polyps. AEA = anterior ethmoidal artery; CT = computed tomography; FS = frontal sinus; MS = maxillary sinus; NS = nasal septum; OC = olfactory cleft; OW = orbital wall; PEA = posterior ethmoidal artery; REAH = respiratory epithelial adenomatoid hamartoma; SS = sphenoidal sinus.

edematous polyps' recurrences. These recurrences could actually be the consequence of residual spots of nonolfactory mucosa in the EC which could not be removed at primary surgery due to anatomical difficulties. Bassiouni et al.[3] found, during revision surgeries, recurrent polyps stemming mostly from the frontal sinus area (55%) or the EC (37%), while there were only 2.4% emanating from the OC. This huge difference could be related to incomplete removal of nonolfactory mucosa inside the anterior ethmoid of the EC during the first procedure, given that patients included in their study were referred for recurrence after functional endoscopic sinus surgery (FESS) with middle turbinate preservation in 100% of the cases.

Nasal polyposis has been shown to be frequently associated to REAH in revision surgery.[5,6] While edematous polyps mainly originate from the EC, REAH are mainly observed inside the OC.[17–20]

Clinically, patients with REAH exhibit similar symptoms to those with CINP, such as nasal obstruction, nasal discharge, facial pain, facial pressure, headaches, olfactory impairment or loss. CINP and REAH can be distinguished thanks to their endoscopic features: REAH is often asymmetrical or unilateral nasal masses of varying sizes, with a slight cerebriform aspect, fleshy to firm, pinkish or sometimes yellowish and appearing fleshier than CINP.[21] However, pathological analyses are required to distinguish CINP from REAH.

Our previous findings suggested that REAH could be considered as induced benign tumors associated to severe or advanced NP disease,[6] as REAH is a benign proliferation of the surface respiratory epithelium which folds like pseudo-glands into the submucosa.[11] Its formation seems to be induced by long-lasting and severe local inflammation[6] but it remains unknown why some patients with NP develop REAH and others do not. The chronic inflammatory process within the OC may induce histological damages to the olfactory epithelium in patients with longstanding NP. The olfactory mucosa could consequently be damaged and slowly replaced by respiratory epithelium[22] from which would REAH develop.

In our series, the mean interval between primary nasalization and revision surgery was nine years. The longest interval was more than 21 years in this series. A shorter time to recurrence requiring a revision surgery was found in cases with middle turbinate sparing and advanced polyps stage. We suggest that the middle turbinate resection leads to better control of the EC and more complete resection of the ethmoidal nonolfactory mucosa. Masterson et al.[23] reported a revision surgery in about 4% at only 36 months after extensive sinus surgery, while the UK national audit[24] reported a 12.3% rate at 36 months when only anterior ethmoid cells were accessed. When compared to functional ethmoidectomy, nasalization offers a better relief in nasal complains and has already shown a lower polyp recurrence rate at 5-year follow-up (22% vs. 58%).[25]

The aim of surgery for NP should be to completely remove the nonolfactory mucosa of the ethmoid. This objective seems, however, unattainable if one considers that olfactory and nonolfactory mucosa are mixed up in the olfactory cleft. This may actually be an explanation why the OC is the main site of recurrence of NP after radical ethmoidectomy.

Limitations

The REAH concept is relatively new and was paid attention at the beginning of the 2000s. Thus, the pathological diagnosis might be biased due to lack of knowledge on this entity. However, the pathological diagnosis of REAH was highly paid attention by pathologists with great knowledge of REAH's histological features since 2003 in our institution. Moreover, our previous study showed a strong relationship between the presence of REAH in the OC and the duration of NP, duration of chronic nasal symptoms, and any history of previous sinus surgery in bivariate analysis.[6] It means that REAH is less frequently observed in patients with NP at the primary surgery. Further studies have to be carried out to reinforce these findings.

CONCLUSION

Complete removal of the nonolfactory mucosa of the ethmoid seems to prevent or delay recurrence of nasal polyposis. Recurrences after radical ethmoidectomy appear mainly in the OC and can develop under three different histological presentations: classical inflammatory nasal polyps, respiratory epithelial adenomatoid hamartoma, or a combination of both lesions.

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