NASAL-SINUS POLYPOSIS: CLINICAL-CYTOLOGICAL GRADING AND PROGNOSTIC INDEX OF RELAPSE

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This longitudinal and prospective study aimed at investigating the influence of some parameters, including nasal cytology and clinical findings (such as asthma, atopy, acetylsalicylic acid (ASA) sensitivity, ASA associated with asthma), as risk factor of post-surgical relapse of nasal-sinus polyps. One hundred sixty-one consecutive patients (92 males and 69 females, mean age 47 years), affected by bilateral nasal polyposis and who had undergone surgical nasal polipectomy (endoscopic FESS), were examined post-surgically at least every 6 months for a period of 10 years. Endoscopic exam and nasal cytology exam were carried out on all patients and their case histories were carefully examined. The association eosinophilic-mast cell cellularity and the contemporary presence of asthma + ASA sensitivity showed the highest level of relapse (OR 4.5). In conclusion, cytological data in association with certain clinical parameters can predict a "high risk" prognosis of relapse.

Nasal polyps (NP) represent a common benign disease affecting 4% of the general population (1). Although many authors have investigated the disease using different methodological approaches, today the multifactorial etiology is still unclear (2-10). Therapeutically, NP presents numerous unknown factors, since there are no shared standardized strategies for its cure (11-12). Although new topical or systemic corticosteroids represent the therapy of choice in NP (13-15), an important percentage of patients resort to surgical treatment, especially when nasal respiration must be restored and for the prevention of complications (16-17). Much more problematic is the management of patients with relapsing polyps. In fact, in spite of the progress made in micro-endoscopic surgery, the percentages of post-surgical relapses vary between 23 and 87% (18-23). This leads to hypothesize that the risk of relapse is not associated with the type of surgical procedure, but to factors that are only partially known. Many studies have sought to identify the "negative" prognostic factors which cause post-operative relapses of nasal polyps, some of which have been demonstrated to be non-significant (age, sex, nasal septum deviation, atopic state, type of surgery) (24). Some significant parameters, not shared by all, include asthma, intolerance to *acetylsalicylic* acid (ASA) and NSAID, number of polyps, percentage of eosinophils in the chorion, previous nasal polypectomies, Widal's syndrome,

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mast cell localization in polyps, and the correlation between increased IgE levels and eosinophilia (25-30).

The present study is therefore aimed at investigating the influence of some parameters, including: nasal cytology and clinical findings (such as asthma, atopy, ASA sensitivity, ASA associated with asthma), as risk factor of post-surgical relapse of nasal-sinus polyps. Consequently, the second aim is to obtain a Clinical-Cytological Grading (C.C.G.) system for drawing-up a Prognostic Index of Relapse (P.I.R.) score.

Thus, the objective of the C.C.G. and the P.I.R. scores would:

- guide The Otolaryngologist to a more rational approach in the medical-surgical treatment of NP and its follow-up.
- provide the patient with a P.I.R. in order to follow the evolution of the disease, avoiding false expectations of a "definitive" recovery, and obtaining from the patient utmost adherence to future ambulatory control visits, and personalized medical treatments, indispensable for the best outcome in controlling the disease.

MATERIALS AND METHODS

One hundred sixty-one (161) consecutive patients (92 males and 69 females) affected by bilateral nasal polyposis, ranging in age between 31 and 68 years (mean age 47 years), were included in this longitudinal and prospective study. All the patients had undergone surgical nasal polipectomy (endoscopic FESS) and were examined post-surgically at least every 6 months for a period of 10 years. Endoscopic exam and nasal cytology exam were carried out on all patients and their case histories were carefully examined. The local Ethics Committee approved this study.

History

A careful general history of each patient was taken, with careful attention to the evaluation of atopy, presence of asthma, aspirin and other NSAID sensitivity, and the number of surgical polipectomy procedures sustained by the patient.

Nasal Endoscopy

The diagnosis of nasal polyposis was made using a fiberoptic endoscope (Vision Science- ENT 2000 of of 3.4 mm diameter).

Nasal Cytology

Cytological samples were obtained by scraping with a Rhino-Probe™. The samples were collected from the medial portion of the inferior middle turbinate. After fixing with absolute alcohol for 3 minutes, the samples were stained using the May-Grünwald-Giemsa (31). Eosinophilic (E) form (Fig. 1A) was diagnosed if nasal eosinophils were >20% of total cells recovered from nasal scraping, including both inflammatory and epithelial cells; Mast cell (M) form (Fig. 1B) was diagnosed if nasal mast cells were >10% of total cells; Neutrophilic (N) form (Fig. 1C) if nasal neutrophils were >50% of total cells; Eosinophilic-Mast Cell (EM) form (Fig. 1D) if concurrent nasal eosinophils were >20%, and mast cells >10% of total cells, according to a previous study (32-33).

Statistical analysis

The "odds" ratio was used for statistical analysis of the data (clinical and cytologic factors) as a measure of risk of post-surgical relapse rate of nasal polyposis. The odds ratio indicates the relationship existing between exposed and not-exposed groups in respect to the probability that the event studied will or will not occur. An odds ratio > than 1: indicates that the probability of an event occurring measured among the "exposed" is greater in respect to the "not-exposed";

odds ratio = to 1: there is no difference between exposed and not-exposed

odds ratio < than 1: the exposure reduces the risk of the expression of the variable in respect to the not-exposed. Increasing values indicate stronger associations. A p value < 0.05 is considered statistically significant.

RESULTS

Of the 161 patients who underwent surgery, 122 (75.7% - 69 males and 53 females mean age 47.7 yrs) were operated only once: 31 of them (25.4%) were allergic; 22 (17.2%) had Widal's syndrome; 27 (22.1%) were ASA sensitive; 40 (41.1%) had asthma; 66 (53.2%) had no sensitivity to ASA nor were asthmatics. Only one patient (0.8%) had asthma and associated allergy to drugs and/or foods. Twenty-three (23) patients (14.2%) (16 male and 7 females, mean age 51 yrs) had undergone 2 surgical procedures, of which 9 (39.1%) subjects were allergic, 5 (21.7%) were affected by Widal's syndrome, 11 (47.7%) had asthma, 6 (26.1%) were ASA sensitive, and 11 (47.8%) had neither asthma nor sensitivity to ASA. Of the ten patients (6.2%) (6

Table I. *Post-surgery relapse determinants in nasal polyposis.*

Risk factors	Odds ratio	p-value	Risk
eosino – mast.+ ASA sensitivity + asthma	4.5	0.04	High
Eosinophils-Mast cells	1.6	0.28	Medium
ASA sensitivity + asthma+atopy	1.4	0.23	Medium
Eosinophils-mast cells +asthma	1.2	0.81	Low
Asthma	1.2	0.72	Low
ASA sensitivity + asthma	1.1	0.82	Low
Atopy	1.1	0.82	Low

Table II A. *Clinical factors associated with relapses.*

Clinical factors	% Relapse	N. surgeries	Score
ALLERGY	26.1	23	3
ASTHMA	23.1	26	2
ASA SENSITIVITY	0.0	5	1

Table II B. *Cytological factors associated with relapse.*

Cytological factors	% Relapse	N. surgeries	Score
EOSINOPH-MAST.	32.1	28	4
EOSINOPHILS	23.3	90	2
NEUTROPHILS	21.7	23	1
MASTCELLS	21.1	19	1

male and 4 females, average age 51) who had three surgical procedures, 4 (40%) were allergic, 2 (20%) were affected with Widal's syndrome, 5 (50%) had asthma, 2 (20%) were ASA sensitive, and 5 (50%) had neither asthma nor ASA sensitivity. Only four patients (2.4%), 1 male and 3 females (mean age 34.7 yrs) had undergone 4 surgical procedures. Of these, 1 (25%) was allergic, 1 had Widal's syndrome (25%), 2 (25%) had asthma, 1 (25%) was ASA sensitive, and 2 (50%) had neither asthma nor ASA sensitivity. Finally, only 2 (1.2%) of the patients had undergone 5 surgical procedures (1 male and 1 female, average age 45 yrs). Of these 1 (50%) was allergic, 1 had Widal's syndrome (50%), and both (100%) had asthma.

Nasal cytology

Of the 122 patients who had undergone just one surgical intervention of polypectomy 69 (57.0%) had E form, 19(15.7%) EM form, 18 (14.9%) N form, 15 (12.4%) M form. Of the 23 patients who had undergone 2 surgical interventions of polypectomy the E form was found in 15 (65.2%), 4 (17.4%) had EM, 1 (4.3%) had N, and 3 (13%)

Table III A. *Possible combinations between clinical factors.*

Clinical factors	% Relapse	N. surgeries	Score
ASA – ASTHMA – ALLERGIC	42.9	7	6
ASTHMA – ALLERGIC	35.7	14	5
ASA – ASTHMA	26.1	23	3
ALLERGIC	26.1	23	3

Table III B. *Possible combinations between clinical factors and cytologic factors.*

Clinical factors and Cytologic factors	% Relapse	N. surgeries	Score
ASA-ASTHMA – NARESMA	57.1	7	7
ASTHMA – ALLERGIC - EOSINOPHILS	40	10	7
ALLERGIC – EOSINOPHILS	28,6	14	5
ASA-ASTHMA – EOSINOPHILS	14,3	14	5
ASTHMA – EOSINOPHILS	14.3	14	4

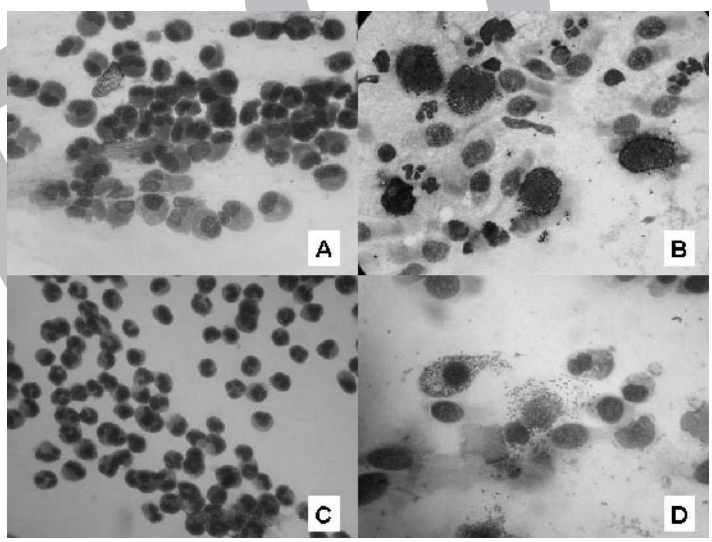

Fig. 1. *Examples of nasal scraping with different cellular predominance.* ***A)*** *eosinophilic typical for NARES;* ***B)*** *mast cell predominance typical for mast cell form of non-allergic rhinitis;* ***C)*** *neutrophilic typical for the neutrophilic form of non-allergic rhinitis;* ***D)*** *eosinophils-mast cells typical for NARESMA.*

cases had the M form. Of the ten patients who had undergone three surgical procedures, 4 (40%) were E, 3 (30%) were EM, 2 (20%) were N, and 1 (10%) was M. Of the 4 patients who had undergone four surgical procedures, in 1 (25%) we found E, 1 (25%) EM e 2 (50%) N. Finally of the 2 patients who had undergone 5 surgical procedures, 50% of the cytology were E and 50% were EM.

Statistical analysis of the data were calculated using odds ratio as a measure of risk of post-surgical

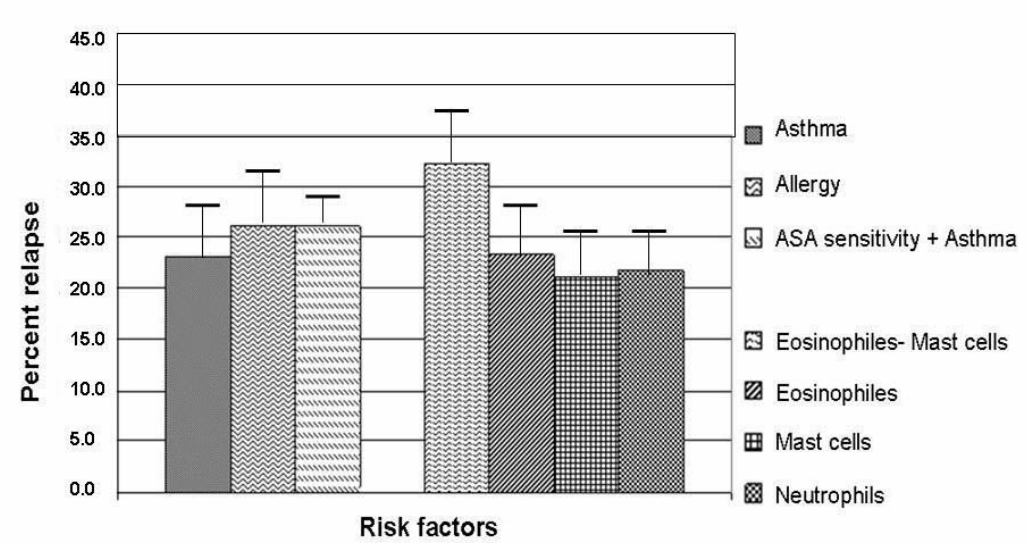

Fig. 2. *Percentages of relapse according to the risk factors considered, such as clinical factors, including asthma, allergic sensitisation, and coexisting acetylsalicylate sensitivity and asthma, or inflammatory factors, based on the predominating cell type. Data are shown as % + s.d.*

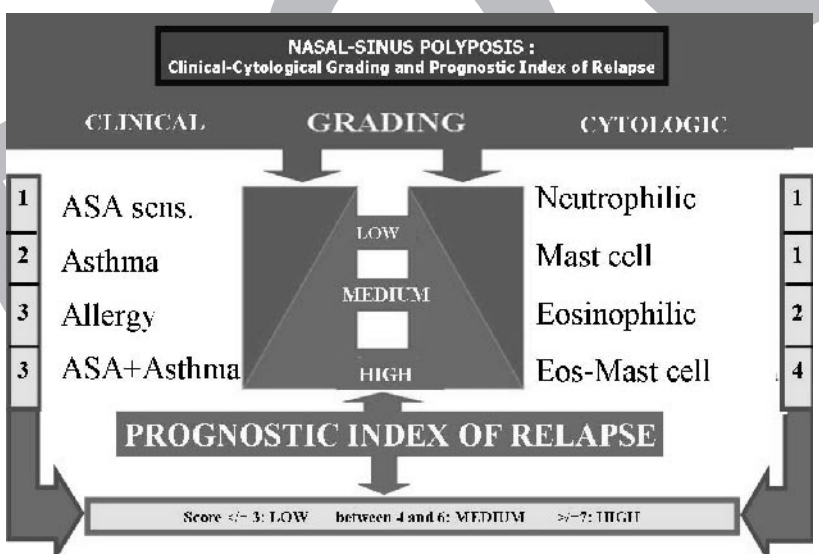

Fig. 3. *Nasal-Sinus Polyposis: Clinical-Cytological Grading (CCG) and Prognostic Index of Relapse (PIR). Each parameter has a value (ranging between 1 and 4). The sum of all parameters corresponds to the grade of possible relapse: low if ≤ 3, medium if between 4 and 6, and high if ≥ 7.*

relapse of clinical and cytological nasal polyps. The correlation between risk factors (clinical-cytological) and prognostic risk of relapse as calculated by odds ratio, and relative index of significance are reported in Table I. The percentages of relapse rate according to the risk factors are reported in Fig. 2.

DISCUSSION

Although in recent years there have been many studies reporting a series of clinical parameters regarding the tendency of post-surgical relapses in nasal polyposis, there are no data that describe the

cellular types which could improve the prognosis of patients undergoing surgery for relapsing nasal-sinus polyposis. With regard to the clinical aspects of this disease which may include atopy, asthma, ASA sensitivity and correlation with the number of post-surgical relapses, we have found, in accordance with other studies (19, 24, 30) a not significant correlation between ASA sensitivity and the number of surgical nasal polypectomies, although the operated subjects on many occasions have presented a higher ASA sensitivity (25.6%) than those who did not undergo surgery for relapsing polyposis (16%). We obtained analogous results when we correlated Widal's syndrome with the number of nasal polypectomies and the presence of asthma with the number of polypectomies. In fact, in the case of Widal's syndrome (12% who had never had surgery, 17% who had undergone one surgical procedure, 23% in the group of patients who had undergone multiple surgeries) as with the sole presence of asthma and allergy, the statistical analysis was not significant. Analysing the correlation between the cell type and recurrence of NP, there were no significant associations, even if the study shed light on the average risk of relapse between subjects that presented the eosinophil-mast cell cellularity (Odds ratio 1.6) (Table I). Also, the comparisons made between clinical parameters (atopy, asthma, ASA sensitivity) with the cytological parameters (neutrophilic, eosinophilic, mast cell, eosinophilic-mast cell) were not significant. Among these, the association eosinophilic-mast cell cellularity and the contemporary presence of asthma + ASA sensitivity showed the highest level of relapse (OR 4.5). Therefore, from a clinical point of view, the contemporary presence of these factors should suggest that the patient, showing this clinical feature, has to be followed with careful attention. Lastly, a medium risk factor of relapse was found in the combination ASA sensitivity + asthma + atopy (OR 2.1), while a low risk factor for relapse was found in the association eosinophile-mast cell + asthma (OR=1.2) and "ASA sensitivity + asthma" (OR=1.1).

In relation to the clinical-cytological studies previously described we have constructed a graph (Fig. 2) where a specific position was assigned to each parameter studied and scored according to their specific weight and correlated them with post-surgical relapses: the clinical-cytological grading (GCC).

The assignment of the specific weights was drawn from the position occupied by the clinical factors and the cytological factors, respectively, from the two decreasing lists of percentages of relapses seen in Table II A/B.

These scores are cumulative since a subject who presents more than one risk factor manifests a greater tendency to relapse. In Table III A/B only those combinations that were observed in more than 5 cases are reported.

From the intersection of the G.C.C. parameters, it is possible to establish a Prognostic Index of Relapse (P.I.R.) quantifying it as low, medium or high as reported in Fig. 3. Therefore, from a clinical point of view, it appears that the highest scores are characterized by the contemporary presence of some risk factors, which implies that each patients should be carefully examined and evaluated considering all these aspects. In addition, we underline the clinically relevant importance of nasal cytology in the follow-up of patients with nasal polyps. Indeed, only nasal cytology allows to diagnose all these forms characterized by the predominance of specific cell types. Thus, only a sure cytological diagnosis allows to precisely define the prognostic factors. Another relevant aspect is represented by the simplicity and low cost of these prognostic factors. In this regard, May-Grunwald Giemsa is surely a quick and cheap method to assess these parameters.

However, it has to be noted that the number of evaluated patients is relatively reduced. This fact represents a limitation of this study, therefore further studies should be performed including greater numbers of patients.

In conclusion, this study highlights that the evaluation restricted only to clinical parameters is not sufficient to express a prognostic judgement with reference to a major or minor probability of a patient with NP to relapse after polypectomy surgery. On the other hand, having cytological data, especially in association with certain clinical parameters, can predict a "high risk" prognosis of relapse. Among the prognostic factors of relapse, bronchial asthma with eosinophil-mast cell cellularity, especially if both are present in the same patient, are the

most relevant. Therefore, it may be suggested that all patients affected with nasal or sinus polyps should undergo a complete pre-operative clinical-cytological assessment and be evaluated according to the G.C.C. proposed in this study. Once the I.P.R. is identified, the patient should be informed of the possible prognostic risks and how to better maximise therapeutic compliance, especially in the post-operative phase.

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