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Histological features and malignant transformation of inverted papilloma

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Abstract Inverted papilloma (IP) is a primarily benign epithelial neoplasm with a propensity to transform to squamous cell carcinoma (SCC). Neither the etiology of IP nor the factors responsible for malignant transformation are fully known to date. A considerable number of histopathological grading systems have been suggested. It was the aim of this study to find histological parameters in IP that allow a prognosis concerning the occurrence of malignant transformation. In a group of 93 cases of IP, the patients' records, histological specimens and a questionnaire were evaluated. Thirteen patients had suffered a recurrence of a previously treated IP. SCC in the IP had been diagnosed in 12 of the cases. The histological specimen showed increased counts of mitosis and dyscariosis in the IP. All other histological parameters did not show a significant difference between the groups. History and symptoms proved to be nonspecific as well. Patients in the group with SCC were significantly older at the first diagnosis of IP than patients without carcinoma. This group also included a higher portion of male patients. Patients fulfilling the named histological criteria combined with male gender and higher age are a high-risk group in the necessary long-term follow-up.

Keywords Inverterted papilloma · Histology · Neoplasm recurrence

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Introduction

Inverted papilloma (IP) or Schneiderian papilloma is a primarily benign epithelial tumor. It makes up 0.5 to 4% of all tumors of the nose and paranasal sinuses [2, 21, 22, 23]. The age distribution shows a peak in the 6th decade. Male patients are more frequently affected, with a gender ratio of up to 3 to 1 [1, 22, 23]. In most of the cases, occurrence is unilateral, but bilateral occurrence has been observed as well [7, 9].

The etiology of IP is unknown. In specimens from surgical removal of the IP, human papilloma virus (HPV) has been detected [1, 4, 5, 6, 8, 12, 16, 17]. Papovavirus has been detected in IP as well [28].

The pattern of growth of this tumor has the potential for local destruction. A tendency to multilocular growth has been reported as well. Two major problems arise in the clinical management of this disease: a tendency to recurrence and the malignant transformation into squamous cell carcinoma (SCC) [22, 23, 26].

The therapy of choice is the radical surgical removal of the IP. The fact that even a radical surgical approach does not guarantee that patients remain free from recurrence warrants a meticulous follow-up of this condition [3, 4, 13, 14, 22, 23, 24].

Today, we do not know any reliable parameter that allows the identification of patients with an increased risk of recurrence or malignant transformation. Recent studies have investigated if such a prognostic parameter could be found in histology [4, 7, 9, 11, 15, 25], infection with HPV [1, 4, 5, 8, 12, 16, 17] or mutations of the p53-suppressor gene [12].

In this retrospective study, we investigated whether there are differences between patients with an uncomplicated course of IP and those patients who suffered a recurrence of the disease or malignant transformation to SCC. We assessed the clinical history, local findings and the results of the pathological examinations of the specimens from surgery.

Table 1 Parameters and classification of histopathological exam of specimens from surgery

Parameter	Classification				
Histological type of epithelium	Squamous	Transitional	Cylindrical		
Number of cell layers of epithelium	Variable	1–7	8–14	15–30	
Dyscariosis	None	Low	Moderate	High	
Stroma-epithelium relation: share of stroma	<30%	30–60%	>60%	Inhomogenous	
Contents of fibers	Low	Moderate	High		
Eosinophilia	None	Minimal	Low	Moderate	High
Infiltration	Minimal	Low	Moderate	High	
Pattern of growth	Multilocular	Solitary	Myxoid	Classification impossible	
Mitosis	Number of mitoses in ten high-power fields				

Materials and Methods

Patients

Between 1978 and 1997, 102 patients with the histologically confirmed diagnosis of IP underwent treatment in the Department of Ear, Nose and Throat Diseases at St.-Jürgenstraße Central Hospital in Bremen, Germany. In 93 of these cases, all necessary data could be retrieved. There were 23 female and 70 male patients (aged 54.9±1.5 years).

Methods

The patients' charts were evaluated. The history, results of the examination on admission and surgical treatment were evaluated. The files of the follow-up clinic, where all patients were examined regularly after discharge, and a questionnaire completed by ENT colleagues who saw the patients later in their practice were evaluated as well. The evaluation covered personal data, history, symptoms, localization of the disease and further development (recurrence, malignant transformation, death from disease). The follow-up was 30±3.37 months.

All histological specimens from surgery were reassessed. In patients with the diagnosis of carcinoma in the IP, the region of the specimen without carcinoma but with IP was investigated. The specimens were stained with hematoxylin and eosin; some were also stained using van Gieson's method. The following parameters were assessed (Table 1).

1. Epithelium. The type of epithelium was classified into squamous cell, transitional cell and cylindrical cell epithelium. The specimens were also classified according to the number of cell layers at the place of the largest extent in the specimen.
2. Mitosis. The number of mitoses was counted with 40-fold magnification of the objective (high-power field). The counts from ten fields were added.
3. Dyscariosis. The frequency of the occurrence of dyscariosis was classified into "none", "low", "moderate" and "high".
4. Connective tissue. The share of connective tissue stroma in relation to epithelial tissue was classified according to its percentage into groups of less than 30, 30 to 60 and more than 60%. In addition, specimens that could not be classified were grouped as "inhomogenous".
5. Contents of fibers. The contents of fibers of the connective tissue stroma were classified as "low", "moderate" or "high".
6. Eosinophilia. The frequency of eosinophilic leucocytes among all infiltrative cells was classified as "none", "minimal", "low", "moderate" or "high".
7. Inflammatory infiltration was classified as minimal, low, moderate or high.

Finally, specimens were assessed according to the classification of Luhn and Hörmann [25]. They were classified as "solitary nodal IP", "multilocular nodular IP" and "myxoid IP". A separate group contained specimens where an exact classification was not possible.

Results

Patients

Sixty-eight of the 93 patients evaluated had a first time diagnosis of IP without carcinoma. Thirteen patients had a recurrence of IP after surgical removal of a previously diagnosed IP. Twelve patients had a squamous cell carcinoma (SCC) in an IP. The share of female patients decreased markedly between these groups (Table 2), but this decrease was not significant (chi-square test).

Recurrence occurred 4.23±1.3 years after the first time diagnosis of IP. Of the 12 cases of SCC, two occurred 1 and 2 years after the first time diagnosis of IP. Two occurred years after the recurrence of IP, 4 and 9 years after the first time diagnosis of IP. The remainder (eight cases) was found together with a first time diagnosis of IP. The average age at the first time diagnosis was the same with patients who had a first time diagnosis of IP or a recurrence of IP. Patients who suffered a carcinoma in the IP were significantly older on first time diagnosis than patients without carcinoma (P=0.018, unpaired, two-tailed t-test).

The diagnosis of IP in the histopathological examination of the surgically removed tissue was a surprise in some cases where there was no clinical suspicion pre- or intraoperatively. There were also cases where IP had been diagnosed preoperatively by biopsy of a clinically suspicious lesion. However, many patients had been referred for surgery of IP after a diagnostic biopsy or nasal surgery

Table 2 Number of patients, age and gender distribution of the investigated patients in their respective groups

Group	Number of patients	Female (%)	Age at first diagnosis (years ± SEM)
First time diagnosis of IP	68	29	53.4±1.7
Recurrence of IP	13	15	53.8±4.0
Carcinoma in IP	12	8	63.8±3.1

had been performed elsewhere. Hence, it is not possible to determine the share of patients retrospectively that would have been diagnosed correctly as IP from the clinical aspect alone.

From the eight cases of synchronous carcinoma, in one case the preoperative clinical situation could not be assessed in retrospective analysis. In two cases, the correct diagnosis of carcinoma in IP had been obtained by preoperative biopsy. However, in five cases, preoperative biopsy resulted in the diagnosis of IP, and the carcinoma in the IP was not revealed until histopathological exam of the surgically removed tissue was performed postoperatively.

Of the four cases of metachronous carcinoma, two cases were diagnosed correctly preoperatively as carcinoma in IP. In the two remaining cases, the clinical diagnosis had been recurrence of IP and no biopsy had been performed. Here, carcinoma in the IP was not revealed until histopathological exam of the surgically removed tissue was performed postoperatively.

Symptoms

The main complaints were nasal obstruction, rhinorrhea, impaired sense of smell and pain (Table 3). No significant difference between the groups was found for the frequency of a symptom. The duration of symptoms prior to diagnosis was 24.7±3.1 months for the first time diagnosis of IP, 15.2±6.4 months for recurrence of IP and 23.8±8.2 months for carcinoma in the IP (all values: mean ± SEM). The difference between the groups was not significant. In all groups, there was also a portion of patients without complaints. This share was comparably high (23.1%) for patients with a recurrence of IP.

Table 3 Frequency of symptoms prior to diagnosis (all values: percentage of all patients in the respective group)

Symptom	First time diagnosis of IP	Recurrence of IP	Carcinoma in IP
Nasal obstruction	82.4	61.5	75.0
Rhinorrhea	19.1	23.1	0.0
Impaired sense of smell	17.6	0.0	16.3
Pain	11.8	0.0	16.9
Feeling of pressure	7.4	15.4	8.3
Epistaxis	8.8	0.0	25.0
Diplopia	4.4	0.0	8.3
None	5.9	23.1	8.3

Table 4 Localization of IP or carcinoma in IP (all values: percentage of all patients in the respective group)

Location	First time diagnosis of IP	Recurrence of IP	Carcinoma in IP
Ethmoid sinus	66.2	46.2	66.7
Maxillary sinus	39.7	38.5	41.7
Frontal sinus	11.8	23.1	16.7
Nasal cavity	20.6	15.4	16.7
Concha	10.3	15.4	41.7
Sphenoid sinus	5.9	0.0	16.7
Nasal septum	2.9	7.7	0.0
Nasal vestibulum	0.0	0.0	0.0

Localization

The local distribution of occurrence of IP, recurrence of IP or carcinoma in the IP in the nose and paranasal sinuses was compared (Table 4). There was no significant difference in the topographic distribution of the disease between the groups.

Histology

The histopathological examination of the specimens did not reveal any statistically significant difference between the groups for the classification of the epithelium, the number of cell layers, the stroma-epithelium ratio, the contents of fibers, eosinophilia, growth pattern or infiltration (Table 5). The number of mitoses did not differ significantly between the first time diagnosis of IP and the recurrence of IP. However, in comparison with both of these groups, there was a significantly increased number of mitoses in IP with squamous cell carcinoma ($P<0.001$, ANOVA). The classification of dyscariosis (Table 6) showed that the share of moderate and high dyscariosis was significantly higher in IP with squamous cell carcinoma than in first time IP or recurrence of IP ($P<0.00001$, chi-square test).

Discussion

The age and gender distribution of our groups of patients reflects the data of the existing literature very well [1, 11, 22, 23, 27]. The preferred sites of IP were the ethmoid and maxillary sinus region [1, 3, 22, 23, 7]; an occurrence at the nasal septum was infrequent [3]. The main symptoms were nasal obstruction, rhinorrhea, impaired sense of smell and pain [3, 7, 15]. A considerable part of the patients (23.1%) in whom a recurrence of IP was diagnosed did not have any symptoms at all. In addition to the fact that the symptoms are not very specific, their absence or presence is not a reliable parameter for the management of IP [24].

In 12 out of 93 patients, we found a SCC in the IP. This rate is consistent with the literature [1, 10, 13, 15]. Patients with SCC in the IP were older [1] and more frequently of male gender [24]. In eight of these cases, the carcinoma was diagnosed simultaneously with the IP. In four cases only, carcinoma developed later. This ratio of synchronous and metachronous occurrence of SCC in the IP is in perfect accordance with the literature [23]. SCC is known to occur preferably synchronously with IP. Metachronous carcinoma occurs less frequently [11, 13, 24].

Table 5 Histopathological parameters not differing significantly

Parameter	Absolute number of patients classified in the subgroup		
Number of cell layers of epithelium	First time diagnosis of IP	Recurrence of IP	Carcinoma in IP
Variable	0	1	1
1–7	29	2	2
8–14	20	5	3
15–30	19	5	6
Stroma-epithelium-ratio (stroma)	First time diagnosis of IP	Recurrence of IP	Carcinoma in IP
0–30%	35	5	4
30–60%	19	3	6
>60%	14	4	2
Inhomogenous	0	1	0
Contents of fibers	First time diagnosis of IP	Recurrence of IP	Carcinoma in IP
Low	43	8	4
Moderate	18	3	7
High	7	2	1
Eosinophilia	First time diagnosis of IP	Recurrence of IP	Carcinoma in IP
None	33	6	7
Minimal	16	5	4
Low	11	1	1
Moderate	6	1	0
High	2	0	0
Infiltration	First time diagnosis of IP	Recurrence of IP	Carcinoma in IP
Minimal	6	0	0
Low	35	6	8
Moderate	19	5	3
High	8	2	1
Pattern of growth	First time diagnosis of IP	Recurrence of IP	Carcinoma in IP
Multilocular	22	3	1
Solitary	16	0	1
Myxoid	28	10	7
Classification impossible	2	0	3
Type of epithelium (1)	First time diagnosis of IP	Recurrence of IP	Carcinoma in IP
Squamous cells	42	9	8
Transitional cells	31	5	5
Cylindrical cells	4	1	1

(1): Patients could be grouped into more than one subgroup

Table 6 Significantly differing histopathological parameters

Parameter	Patient group		
Mitosis	Average number of mitosis per field of vision		
IP	First time diagnosis of IP	Recurrence of IP	Carcinoma in IP
Mean ± SEM	6.6±0.9	9.5±2.4	23.7±4.8
Dyscariosis	Absolute number of patients		
	First time diagnosis of IP	Recurrence of IP	Carcinoma in IP
None	50	4	2
Low	14	8	2
Moderate	2	1	1
High	2	0	7

Today, we have no reliable parameter for the prognosis of recurrence or malignant transformation of a diagnosed IP. HPV subtyping was mentioned as a possible prognostic factor [1, 8, 17, 30]. A link between the histological type of papilloma and the HPV subtype has been suggested as well [30]. There is also a lack of reliable histo-

logical parameters. Since they were described by Billroth, papillomatous tumors of the nose have been graded into different systems. Hyams investigated papilloma in 315 patients [15] and made a histological typing into three groups: firstly, the inverted papilloma with a histological inversion of the squamous cell epithelium into underlying stroma; secondly, the fungiform papilloma with epidermoid epithelium and exophytic growth; finally, cylindrical cell papilloma with the respective epithelium. He then associated a different clinical behavior with these histological subtypes. The first group was associated with occupation of the nasal space and nasal obstruction. The fungiform papilloma was associated with occurrence on the nasal septum of younger patients and epistaxis, while the other two occur on the lateral wall of the nasal cavity and in the paranasal sinuses. No difference in recurrence was found, but there was never malignancy in the fungiform papilloma. Because of these differences, Hyams suggested treating these three groups as totally different entities. However, Kelly et al. [19] found inverted papilloma on the nasal septum. Because of their tendency to recur, they suggested not classifying papilloma of the nasal septum separately from papilloma of the lateral wall of the nasal cavity or paranasal sinuses. In this study, we could not find any relation between localization, symptoms and recurrence. Kaufman et al. [18] found an increased rate of recurrence and malignancy for papilloma with cylindrical cell epithelium. This finding cannot be confirmed by our data. Luhn and Hörmann [25] grouped IP into a "solitary nodal IP" with a nodular smooth surface, a "multilocular nodular IP" with a verrucous flat growth and a "myxoid IP" that forms narrowing masses in the nasal cavity. The first two groups were found on the nasal septum, while the latter was found on the lateral wall of the nasal cavity and in the paranasal sinuses. It was only this last subtype that showed a malignant transformation in their study. However, we found a case of multilocular nodular IP and a case of solitary nodal IP, both with a malignant transformation.

Buchwald et al. [7] classified IP according to the epithelium: squamous cell epithelium, metaplastic epithelium und glandular epithelium, as well as combinations of the three. They did not find any relation between histological findings (type of epithelium, rate of mitoses) on the one hand, and clinical development (recurrence, malignant transformation) on the other hand.

Lawson et al. [23] did not find any relation between atypical cells and recurrence. In their study, tumor size was an important factor for prognosis. Batsakis and Suarez suggested that "obvious keratosis" might be an "ominous sign", but they conceded that there was no strong predictive factor from histology [2].

A subtyping into hard and soft papilloma because of the stroma-epithelium ratio [20] did not show any clinical consequence with our patients, nor did a classification according to infiltration or eosinophilia.

Christensen and Smith [11] found increased recurrence and malignant transformation with endophytic growth of the papilloma. These did not have a significantly increased rate of cellular atypia and mitoses. However, cellular atypia was related to an increased incidence of recurrence of IP [29]. An increased rate of mitoses or dyscrioses in the IP was the only parameter associated with an increased rate of malignant transformation in our study.

This does not have consequences for patients with synchronous SCC, because malignant transformation already has occurred and will be diagnosed by routine histopathological examination. In all other cases, these parameters might help to identify a high-risk group for a metachronous SCC that needs particular attention in follow-up.

Conclusion

In this study, we investigated the different histological parameters that have been proposed in the literature to classify IP. All of them have been applied on different cohorts of patients. In our study, these criteria were applied in parallel to one cohort of patients. An increased rate of mitoses and dyscrioses in the IP were the only parameters associated with an increased rate of malignant transformation. All other parameters did not show any association with the clinical fate of a patient. In the patients' histories, there was no specific symptom that could be an adequate warning either for IP or for recurrence or malignant transformation. On the contrary, the symptoms found were nonspecific. A considerable share of patients with recurrence did not have any symptoms at all. Clinical assessment and preoperative biopsy of suspicious lesions revealed only two out of four metachronous and only two out of seven synchronous carcinomas in IP. The remaining carcinomas in IP were identified by a postoperative histopathological examination of all tissue that had been removed during surgery. This warrants the complete histopathological examination of all tissue that was removed from the nose or paranasal sinuses during surgery.

Secondly, a meticulous follow-up for patients with a known IP is necessary. Symptoms are not reliable help in assessing the development of a case.

Thirdly, a group with an increased risk of malignant transformation of IP could be identified. Patients of higher age with a first diagnosis of IP and with high rates of mitoses and dyscarioses have an increased risk of developing a malignant transformation of the IP.

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