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Inverted Sinonasal Papilloma – A Report of 31 Cases and Review of the Literature

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A B S T R A C T

Inverted papilloma is an epithelial neoplasm of the lateral nasal wall and adjacent sinuses characterized by a marked propensity for recurrence and a significant association with carcinoma In this retrospective study we present 31 cases treated by our departments between 1982 and 1999. The aim was to compare our results to those of other authors especially regarding surgical management. The male to female ratio of these patients was 2:1 and most patients were in the 6th and 7th decades of life. Conservative surgery was used in most cases as the initial treatment. The overall recurrence rate was low and there were 3 cases associated with carcinoma. We conclude that the results of conservative surgery in selected cases are comparable to those using radical methods. A review of the literature is presented and particular attention is dedicated to the literature concerning analysis of p53 expression, HPV and Epstein-Barr infection and apoptosis in inverted papilloma.

***Key words**: head and neck tumors, nasal tumors, inverted papilloma*

Introduction

Inverted papilloma of the nose and paranasal sinuses is a rare tumor of the head and neck region and constitutes 0.5–4%[15,18] of all tumors of the nose and sinuses. Nevertheless, for decades it has been the subject of interest of many re-

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searchers due to several peculiar characteristics. It has been noted that this lesion has a marked tendency to recur as well as a significant association with squamous cell carcinoma of the paranasal sinuses[15,28]. The reasons for such a behavior have been extensively examined and clarified to some extent but the real etiology of this lesion remains obscure.

Due to insufficient knowledge a number of different names were used for this lesion (papillary sinusitis, papillary fibroma, papillomatosis) and it was classified as an inflammatory process as well as a neoplasm. Hyams[15] made a precise histopathologic description and classification of inverted papilloma in 1971 when he published an extensive study on the subject. Histological, the tumor consists of a vascular stroma, often accompanied by inflammatory reaction, covered with epithelium, which inverts into the underlying stroma. The epithelium is separated from the stroma by a basement membrane and may be of the squamous cell but also columnar or mixed type.

Material and Methods

A retrograde search of patient charts in the archives of the Department of Otorhinolaryngology of the University Hospital Center »Zagreb», Zagreb and the Department of Otorhinolaryngology of the University Hospital »Osijek«, Osijek was performed. In the period from 1982 to 1999 there were 31 cases of inverted papilloma treated by our departments. Some of the patients have been repeatedly hospitalized for recurrent disease. In this study we analyzed the cases by sex and age distribution, symptoms and anatomic site of the disease, the type of operative treatment, the association with carcinoma and the frequency of recurrence.

Results

Age and sex distribution

Of the 31 patients included in our study there were 21 men (68%) and 10 women (33%).

The age of the patients varied from 18 to 70 years at the time of diagnosis. Most of the patients were in the 6th (32%) and the 7th (26%) decades of life. The minimum follow-up was 3 years for the patients included in the study.

Symptoms

The most frequent complaint of our patients was nasal obstruction, usually unilateral (80%). In the majority of cases the patient reported at least one additional symptom. The second most frequent was nasal discharge (45%), more often bloody than purulent. 38% of patients complained of pain (headache or localized facial pain) while epiphora, proptosis and sore throat were rarely en- countered. In our series both proptosis and epiphora were present in a patient with malignant alteration.

Location and histopathology

At the time of diagnosis inverted papilloma was most frequently found in the nose (29 out of 31 patients). In the majority of the patients the tumor extended to the adjacent areas: the maxillary sinus in 17 cases and the ethmoid sinus in 15 cases. The presence of a tumor mass in the epipharynx was found in 3 patients while extension in the sphenoid sinus was an infrequent finding present in only two cases.

The extension of the disease was evaluated preoperatively by clinical examination followed by radiography of the sinuses and/or CT scan. In one case ultrasound examination was used for evaluation of ocular pain.

Surgical procedures

The procedures presented here include both those performed for initial treatment as well as treatment of recurrent disease. Most frequently the patients were treated by polypectomy or FESS (Functional Endoscopical Sinus Surgery) (51% of cases). In 9 cases a combination of FESS and Caldwell-Luc operation was performed, while 7 patients were treated by Caldwell-Luc operation alone. Lateral rhinotomy with medial maxillectomy was used in only one case and radical maxillectomy in two. Both of the patients treated with radical maxillectomy had malignant disease; in one of these two cases, radical maxillectomy was accompanied by exenteration of the orbit.

Incidence of recurrence and malignancy

Five patients experienced recurrent disease during follow-up. In the cases of benign disease usually the patients had a single recurrence but one patient had two. Two cases of recurrence were usually associated with malignant alteration.

At the time of diagnosis inverted papilloma was associated with squamous cell carcinoma in three cases. Two patients suffered of recurrent disease and eventually died while one patient treated for inverted papilloma associated with carcinoma was disease free during follow-up (3 years). One patient included in this study died of malignant disease of different origin (carcinoma of the lung).

Discussion

Inverted papilloma of the nose and paranasal sinuses is a rare tumor of the head and neck region and thus a series of 31 patients represent an interesting study population. Because of some peculiar characteristics like the high recurrence rate and the association with carcinoma, inverted papilloma remains a poorly understood pathological entity. This makes the therapeutically approach for this disease a matter of controversy.

In most retrospective studies which included a significant number of patients the mean age of the patients was between 52 and 59 years with significantly higher incidence in males (male to female ratio about 4:1 to 3:1)[20,26,29]. In our study the mean age was 52.2 years and the male:female ratio was 2:1.

Similarly to other tumors of this region, inverted papilloma causes non-specific symptoms and the most frequent are unilateral nasal obstruction and mucopurulent discharge[18,29]. Epistaxis, unilateral facial pain or epiphora are more rarely seen. The last two symptoms indicate an extension to the orbit but this is not necessarily associated with malignant alteration[18]. The tumor usually fills the nasal cavity and appears as a firm polypoid mass, usually more vascular then the softer inflammatory polyps. The inflammatory polyps may be present simultaneously, which may cause errors in diagnosis even after biopsy due to an inappropriate sample choice. Inverted papillomas typically arise from the lateral nasal wall in the area of the middle nasal concha and the middle meatus. Rare location as the inferior nasal concha, the vestibulum of the nose and the nasal septum have also been described. In accordance to the primary site of this tumor, the maxillary sinus and the ethmoid cells are the most important sites of extension[20,26]. The presence of tumor mass in the frontal and sigmoid sinuses indicates more advanced disease, which has implication in the choice of the appropriate surgical approach. The significant number of cases of advanced disease at time of diagnosis and the difficult approach to some of the involved areas are considered the most important reasons for the high rate of recurrence observed[19,27].

The most frequent symptom reported by our patients was nasal obstruction

which is consistent with the results of other authors[18,26,29]. Often the patients complained of headache, which might be explained by inadequate ventilation of the sinuses. Some authors report that ocular symptoms and bone erosion seen on radiography or CT is not necessarily a sign of malignant disease[18]. In our cases only one patient had epiphora and this was in association with malignant alteration.

The lateral nasal wall as the most frequent site of involvement is also confirmed by our study.

The rates of recurrence reported in the literature vary from 13 to 70%. Ringertz[27] was the first who identified incomplete resection as the primary reason for recurrence in 1938. Some authors tried to investigate other characteristics that might indicate a tendency to recur but neither the histological features nor the clinical characteristics could be related to the rate of recurrence[15]. Recent studies have concentrated on the role of genetic changes and HPV infection on the recurrence rate and malignant alteration of inverted papilloma. No significant correlation with the rate of recurrence could be demonstrated but it appears that mutations of genes involved in carcinogenesis and HPV infection might play a role in inverted papillomas associated with malignancy as will be explained later. These observations have led to the conclusion that the tendency to recur and the association with carcinoma are two separate characteristics of inverted papillomas having different causes. This is consistent with the observation by Hyams that a high incidence of recurrence is independent of malignant alteration[15]. In our study the incidence of recurrence was relatively low despite of the conservative therapeutic approach adopted in most cases.

10–15% of inverted papillomas are reported[25,29] to be associated with squamous cell carcinoma although rates as high as 50% have been found[31]. Squamous cell carcinoma can be associated with inverted papilloma in two ways: in the majority of cases it is present simultaneously with the inverted papilloma either as a small focus or as the dominant part (synchronous carcinoma), in the remaining cases the carcinoma appears in the area where an inverted papilloma has previously been resected (metachronous carcinoma). Considering the close association of these two entities it has been speculated that inverted papillomas might act as precursor lesions for the development of malignant squamous cell carcinoma. New studies have therefore tried to elucidate the etiology of both benign inverted papilloma as well as carcinoma associated with inverted papilloma in order to better understand the nature of their association. The understanding of the crucial steps in malignant alteration could help us identify the patients at higher risk for developing a malignant change.

Recognizing the role that the tumor suppressor p53 plays in a large number of human cancers[9] the possible role of p53 in inverted papilloma has also been investigated.

In various recently published papers the presence of mutated p53 has been demonstrated in inverted papillomas[7,8,11,16,24]. Due to its longer half-life the mutated form of p53 protein can be detected by immunohistochemistry but methods for direct mutation detecting such as PCR have also been used[4,10]. The frequency of p53 mutations is significantly higher in inverted papillomas associated with malignant change (either synchronous or metachronous carcinoma) compared to the benign forms. The frequency of overexpression of p53 in benign papillomas varies depending on the study from 0–26% but there is always a significant difference compared to those associated with carcinoma[4,7,24]. Interestingly, the frequency of p53 overexpression in squamous cell

carcinomas of the maxillary sinus not associated with inverted papilloma is also reported in a wide range. Some authors did not find any p53 overexpression in these carcinomas and hypothesized a different pathogenesis of carcinomas associated with inverted papillomas compared to those that arise independently[4]. On the contrary, some authors report even higher frequencies of p53 overexpression in maxillary sinus carcinomas not associated with inverted papilloma. The association of p53 mutations and the tendency to recur or advanced stage of disease at the time of diagnosis could not be demonstrated. This is in accordance with the observation that the tendency to recur in inverted papillomas is independent of malignant alteration[15].

Many authors[1,2,11] have investigated the presence of HPV in inverted papilloma. The frequency of HPV infection in inverted papillomas detected by in situ hybridization varies from 20–50%[23] while some authors report an incidence of 6–38% using PCR[1,4]. Some studies report a significant difference in the frequency of HPV infection between benign inverted papillomas and those associated with malignancy[4]. It has been noted that HPV types 16 and 18, known as the primary cause of malignant degeneration in other human cancers, are more frequent in papillomas associated with SCC. When an immunohistochemistry for p53 was done on the same specimen an inverse relationship between p53 overexpression and HPV infection was found[23]. This can be explained by the fact that viral protein E6 binds to p53 protein inactivating it and probably stimulates its degradation (thus preventing its detection by immunohistochemistry).

Epstein-Barr is a DNA virus that acts as a polyclonal activator of B-lymphocytes but can also transform B-cells in vitro. It is considered to be an important factor in the etiology of several types of head and neck tumors namely undifferentiated nasopharyngeal carcinoma but with significant geographical differences. The incidence of latent Epstein-Barr infection in inverted papilloma and undifferentiated sinonasal carcinoma has been investigated in the past few years but the published papers reported completely different results. MacDonald et al.[21] report that most of the cases of inverted papilloma have EBV-DNA detected by PCR compared to nasal polyps in which EBV-DNA was not found using the same technique. In a later paper the authors used an additional technique (in situ hybridization) and found only 8% incidence of EBV infection by PCR and 0% using in situ hybridization[12]. The difference of results between these two techniques is explained by the fact that EBV-DNA may be incorporated in lymphocytes present among tumor cells and is detected by PCR. In situ hybridization detects only viral DNA present in tumor cells which may be relevant for neoplastic growth. Thus, it can be concluded that the role of EBV in the etiology of inverted papilloma remains controversial but some of the differences in results might be due to technical or epidemiological differences.

Tobacco smoking has a powerful carcinogenic effect and is recognized as an important factor in the pathogenesis of cancer including that of the head and neck. A possible role of smoking in the pathogenesis and malignant alteration of inverted papilloma has not been demonstrated but it appears that the patients that smoke could have an increased incidence of recurrence[16]. Overexpression of the p53 was associated with heavy smoking in patients treated for inverted papilloma[7]. The association of professional exposure to gases, vapors and aerosol as possible carcinogens and the increased incidence of inverted papillomas, as reported in one paper, is not fully understood[6].

Apoptosis was investigated in many types of cancer since it is possible to speculate that this mechanism may act as a »barrier« against cancer. The role of apoptosis was investigated in inverted papilloma where an increased rate of apoptosis was found in comparison with normal mucosa[13,24]. The incidence of apoptosis was not associated with p53 mutations, which may indicate that p53 does not play a major role in the control of apoptosis in inverted papilloma[24].

A recently published paper gives important insight into the problem of inverted papilloma as a possible precursor lesion for carcinoma by asking two questions: is inverted papilloma an example of monoclonal proliferation and are there any genetic alteration in inverted papilloma that are typically found in premalignant lesions of the head and neck? Using analysis of chromosome X inactivation a typical pattern of monoclonal proliferation was found in inverted papilloma. Squamous cell carcinoma arising in inverted papilloma also showed a monoclonal pattern but interestingly the inactivated alleles were not the same, which might indicate that inverted papilloma and the corresponding carcinoma arise from different clones. The authors could not find any genetic changes on chromosome sites 9p, 17p, 11q and 13q by analyzing the samples of inverted papilloma for loss of heterozygosity (LOH). Mutations on these sites are typically seen in premalignant changes of the head and neck and the respective carcinomas. The absence of mutations of these sites in inverted papilloma leads to the conclusion that inverted papilloma does not fit the typical profile of a true premalignant lesion[3].

In our study malignant alteration was seen in three of our patients. All of them had synchronous carcinoma, which means that the carcinoma was present at the time of diagnosis together with the inverted papilloma. Two patients had recurrent disease and died of maxillary carcinoma despite of radical surgical treatment and one patient is disease free after one year of follow-up.

The diagnosis of inverted papilloma is rarely made preoperatively. This pathology is rarely suspected and it is most often confused with inflammatory polyposis. This might partially explain why polypectomy was so often used as the initial procedure in our study.

In the past, as the nature of this disease became better understood along with the understanding that recurrence is mainly due to inappropriate excision, the trend turned toward radical surgical treatment[19,25]. Such an approach must provide adequate surgical exposure of the involved areas. Lateral rhinotomy was therefore proposed as the golden standard in the therapy of inverted papilloma and most authors performed it in the majority of cases[18,25,29]. A comparably radical method, except for the supraorbital cells and the frontal sinus, is the degloving technique proposed by some authors which does not leave a facial scar. After the implementation of FESS many authors tried to define criteria that would permit the use of conservative techniques in selected cases with comparable results in terms of prevention of recurrence[14,19]. With the aid of preoperative CT scanning it would be possible to select patients with disease limited to the middle nasal concha and middle meatus with limited extension to the maxillary sinus and anterior and middle ethmoid cells[22,30]. The use of endoscopic techniques in these patients gives similar results with significantly lower morbidity compared to more radical operative techniques. The latest work on this subject that questions the precancerous nature of inverted papilloma supports this approach. Non-endoscopic techniques that do not offer an adequate exposure (intranasal polypectomy,

Caldwell-Luc operation, Denker operation) are now abandoned and the choice is between endoscopic surgery for limited disease and more radical techniques for advanced disease.

The number of patients with recurrent disease in our study was low and it is not possible to precisely evaluate the role of different surgical techniques in the prevention of recurrence. Nevertheless, it is interesting to mention that all the patients that have not had a recurrence were treated with polypectomy or FESS, which might indicate that a conservative approach could be adequate in patients with benign disease with limited extension.

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INVERTIRANI SINONAZALNI PAPILOM – IZVJEŠĆE O 31 BOLESNIKU I PREGLED LITERATURE

S A Ž E T A K

Invertirani papilom je epitelna neoplazma lateralnog nazalnog zida i susjednih sinusa karakterizirana izrazitom sklonošću ka ponovnom javljanju i značajnom povezanošću s razvojem karcinoma. Ova retrospektivna studija prikazuje slučajeve 31 bolesnika koji su liječeni na našim odjelima u razdoblju od 1982. do 1999. godine. Cilj je bio usporediti naša s iskustvima drugih autora posebno u odnosu na kirurško liječenje. Među ispitivanim bolesnicima omjer muškaraca prema ženama bio je 2:1, i većina njih bili su u 6. i 7. dekadi života. U najvećem broju slučajeva kao inicijalno liječenje pristupilo se konzervativnom kirurškom zahvatu. Ukupna stopa ponovnog javljanja papiloma bila je niska i u 3 slučaja papilom je bio povezan s karcinomom. Autori zaključuju kako su rezultati konzervativnih kirurških zahvata u nekim slučajevima usporedivi s onima gdje su primijenjene radikalne metode liječenja. U pregledu literature posebna je pozornost posvećena izvješćima o utjecaju ekspresije gena p53, infekcijama HPV i Epstein-Barr virusom te apoptozi na razvoj invertiranog papiloma.