

Bacteriology of inverted papilloma*

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Abstract

Background: Inverted papilloma (IP) is a benign lesion of the nasal cavity and paranasal sinuses. The aetiology of IP remains unclear.

Objective: To assess whether the sinonasal bacteriology of patients with IP is different from the bacteriology of chronic rhinosinusitis (CRS) patients and if there are differences between primary and recurrent IP.

Methodology: A retrospective review of patients with IP at a tertiary referral centre. Intraoperative microbiology results from primary and revision IP resections were compared to each other and to published microbiology data from CRS patients.

Results: Twenty-six cases of IP were identified with a total of 83 intraoperative cultures, of which 43 were positive. The most common isolates were coagulase negative *Staphylococcus* (SCN), *Propionibacterium*, *Staphylococcus aureus*, and *Streptococcus*. The trends in the prevalence of isolates were similar to those reported for CRS patients. Additionally, similar bacteriology was identified between primary and revision IP patients.

Conclusion: In our series, the most common bacterial isolates found in IP are similar to those of CRS, as is the prevalence of gram-negative organisms. Additionally, we did not demonstrate a difference between primary and recurrent IP. Our findings suggest that IP does not result from specific sinonasal microbial exposure.

Key words: inverted papilloma, bacteria, gram-negative organisms, coagulase negative *Staphylococcus*, chronic rhinosinusitis

Introduction

Inverted papilloma (IP) is a benign lesion of the sinonasal cavity arising from the Schneiderian membrane of the mucosa. The biological characteristics of IP has been well-documented, including its tendency to recur and its association with squamous cell carcinoma (SCCa)⁽¹⁾. However, the aetiology of inverted papilloma remains unclear. Recently, studies have evaluated the presence of high risk HPV genotypes and the association of HPV with IP although no clear association has been identified⁽²⁻⁴⁾. Additionally, IP has also been found in the setting of chronic

rhinosinusitis (CRS)^(5,6). A recent study by Vorasubin et al.⁽⁶⁾ suggested a history of CRS as a predictor of papilloma subtype. Thus, a possible link may exist between CRS and IP. To our knowledge, there have been no studies evaluating any bacteriological association with IP.

Our study aims to assess the bacteriology of patients with IP and identify any differences between the microbiology of patients with IP and those with CRS, as well as identify differences between primary and recurrent IP.

Materials and methods

We conducted a retrospective chart review on patients with the diagnosis of IP at the Hospital of the University of Pennsylvania and at the Philadelphia Veteran's Affairs Medical Center from 2010-2013. IRB approval was received from the Hospital of the University of Pennsylvania and the Philadelphia VA Medical Center prior to initiation of our study. We included patients with intraoperative culture results available in the study. Cultures were taken from the tissue specimen from the inverting papilloma itself or mucopurulence directly adjacent to the IP. Patients were divided into 2 groups, those with primary IP and those with recurrent IP.

Specimens were examined for presence of organisms on culture, including aerobic/anaerobic, gram-negative/gram-positive, and fungi. In our study, we adopted the approach of Nadel et al.⁽⁷⁾ and Kingdom and Swain⁽⁸⁾ in reporting culture results. We present our results in 1) the number of isolates for a given organism per total number of isolates, 2) the number of positive cultures for a given organism per total number of cultures, and 3) the number of patients with a positive culture for a given organism per total number of patients.

In addition, we conducted a retrospective chart review on a subset of CRS patients with available culture results in 2011-2012 to also compare to published culture results as well as the IP culture results. The main goal of including evaluations of our CRS patients was to ensure no differences in location of study or year of collection, as previous studies were performed several years ago.

Fisher's exact test was used to determine differences between prevalence of gram-negative and gram-positive organisms in IP compared to that of CRS, as well as differences between primary and recurrent IP. Differences were considered statistically significant if $p < 0.05$.

Results

A total of 24 patients met our inclusion criteria. Two patients had 2 surgeries for recurrent papilloma, and thus a total of 26 cases were analyzed, of which 83 cultures were sent. Overall, 43 of these cultures were positive (52%). The breakdown of cultures by location was maxillary (36%), ethmoid (24%), frontal (9%), and sphenoid (12%). Sixty-one total isolates were found. Gram-negative organisms included: *Pseudomonas*, *Enterobacter*, *Serratia*, *Haemophilus*, *Moraxella*, *E. coli*, unspecified anaerobic cocci, unspecified anaerobic rods, and unspecified gram-negative organisms. Gram-positive organisms included coagulase-negative *Staphylococcus* (SCN), *Propionibacterium*, *Staphylococcus aureus*, *Streptococcus*, *Diphtheroids*, unspecified rods, unspecified anaerobic rods, and *Actinomyces*. Lastly, *Alternaria* was

also found. The most common isolates were coagulase negative *Staphylococcus*, *Propionibacterium*, *Staphylococcus aureus*, and *Streptococcus*. Gram-negative organisms were found in 20% of isolates, 14% of total cultures, and 46% of patients. This was not found to be statistically significantly different from that of CRS ($p > 0.05$). The pertinent data for the overall group is outlined in Table 1. Average age for our series was 59 years with a male dominance of cases, representing 69% of all cases, and 63% of patients were current smokers or had a prior history of smoking.

In the primary surgery group, there were 8 patients with 17 cultures, yielding 14 isolates. Nine cultures did not reveal any growth, and thus 8 (47%) cultures were positive. The most common isolates were SCN, *Staphylococcus aureus*, *Streptococcus*, and *Enterobacter*. Table 2 further outlines the data of this group. Gram-negative organisms were found in 21% of isolates, 18% of cultures, and 38% for patients of the primary surgery group. Demographic data bears approximate similarity to the overall group: average age was 58 years, males represented 72% of all cases, and 63% of patients were current smokers or had a prior history of smoking.

In the revision surgery group, there were 18 patients with 66 cultures, yielding 44 isolates. Thirty-one cultures did not reveal any growth, and thus 35 (53%) cultures were positive. The most common isolates were SCN, *Propionibacterium*, *Staphylococcus aureus*, and *Streptococcus*. Table 3 further outlines the data of this group. Gram-negative organisms were found in 20% of isolates, 14% of cultures, and 50% for patients of the revision surgery group. Average age was 58 years, males represented 67% of all cases, and 63% were current smokers or had a prior smoking history.

There were no gram-negative organisms prevalent in either the primary or revision surgery group. The primary surgery group consisted of primarily *Enterobacter* species, but overall the gram-negative organism prevalence remained approximately the same as that of the revision surgery group ($p > 0.05$). Thus, the total prevalence was similar. The revision surgery group had no one major gram-negative organism represented in the isolates, but rather was spread out evenly amongst the various gram-negative species.

Degree of metaplasia and dysplasia on histologic examination was not associated with clinical microbiology reports. IP associated with gram-negative organisms displayed varying levels of dysplasia; three each were negative for dysplasia and squamous metaplasia, while two each showed low-grade dysplasia, moderate dysplasia, and high-grade dysplasia. None of the IP associated with gram-negative organisms were found to show squamous cell carcinoma. There was one case of invasive and in

Table 1. Summary of most common isolates for all patients.

Gram-negatives	Number	Inverted Papillomas			Chronic Rhinosinusitis			
		% Total isolates	% Total cultures	% Total patients	Number	% Total isolates	% Total cultures	% Total patients
<i>Pseudomonas</i>	2	3%	2%	8%	0	0%	0%	0%
<i>Enterobacter</i>	3	5%	4%	12%	1	2%	2%	4%
<i>Serratia</i>	1	2%	1%	4%	1	2%	2%	4%
<i>Haemophilus</i>	1	2%	1%	4%	2	4%	4%	9%
<i>Moraxella</i>	1	2%	1%	4%	3	6%	6%	13%
<i>E coli</i>	1	1%	1%	4%	1	2%	2%	4%
Other	3	1%	4%	4%	4	8%	8%	17%
Total	12	20%	14%	12%	12	24%	24%	52%
Gram-positives								
SCN	14	23%	17%	54%	10	20%	20%	43%
<i>Propionibacterium</i>	9	15%	11%	35%	3	6%	6%	13%
<i>Staph aureus</i>	6	10%	7%	23%	2	4%	4%	9%
<i>Streptococcus</i>	5	8%	6%	19%	2	4%	4%	9%
<i>Diphtheroids</i>	4	7%	5%	15%	3	6%	6%	13%
Other	6	10%	7%	23%	4	8%	8%	17%

SCN = coagulase-negative *Staphylococcus*

situ moderately differentiated, poorly keratinizing squamous cell carcinoma that showed no growth.

We also collected 49 cultures on 23 cases of CRS in 2011-2012 for a total of 51 isolates. In our study, we found gram-negative organisms in 24% of isolates, 24% of cultures, and 52% of patients. The most common gram-negative organisms found were *Moraxella* and *Haemophilus* species, found in 13% and 9% of patients, respectively. Comparison of these results to that of IP is further outlined in Table 1.

Discussion

IP is estimated to account for 0.4%-4.7% of all sinonasal tumours, with an incidence of 0.6-1.5 cases per 100,000 per year⁽⁹⁻¹¹⁾. They have further been characterized by their locally destructive and aggressive behaviour⁽¹¹⁾. Additionally, IPs are concerning for their propensity to recur, ranging from 4.3%-33.3%⁽¹²⁻¹⁶⁾ and a 7-9% risk of malignant transformation to squamous cell carcinoma^(14,17).

The aetiology of these tumours continues to remain unclear.

Table 2. Summary of most common isolates for primary surgery group.

Gram-negatives	Number	% Total isolates	% Total cultures	% Total patients
<i>Pseudomonas</i>	1	7%	6%	13%
<i>Enterobacter</i>	2	14%	12%	25%
Total	3	21%	18%	38%
Gram-positives				
SCN	3	21%	18%	38%
<i>Propionibacterium</i>	1	7%	6%	13%
<i>Staph aureus</i>	3	21%	18%	38%
<i>Streptococcus</i>	2	14%	12%	25%
<i>Diphtheroids</i>	1	7%	6%	13%
GPR NOS	1	7%	6%	13%

SCN = coagulase-negative *Staphylococcus*, GPR = gram-positive rods, NOS = not otherwise specified

Table 3. Summary of most common isolates for revision surgery group.

	Number	% Total isolates	% Total cultures	% Total patients
Gram-negatives	9	20%	14%	50%
Gram-positives				
SCN	11	25%	17%	61%
<i>Propionibacterium</i>	8	18%	12%	44%
<i>Staph aureus</i>	3	7%	5%	17%
<i>Streptococcus</i>	3	7%	5%	17%
<i>Diphtheroids</i>	2	5%	3%	11%
GPR NOS	2	5%	3%	11%
GPR NOS	2	5%	3%	11%
<i>Diphtheroids</i>	1	2%	2%	6%

NOS = not otherwise specified, SCN = coagulase-negative Staphylococcus, GPR = gram-positive rods.

Various studies have reported an association of IP with human papilloma virus (2,3,18,19) but a systematic review by Syrjanen (4) shows wide variability of HPV prevalence. Furthermore, studies have been unable to confirm HPV as the initial cause of neoplastic transformation. However, HPV is unable to infect normal respiratory epithelium because it requires squamous epithelium to penetrate the surface, suggesting an initial inflammatory response with secondary metaplastic change from normal columnar epithelium must first occur (20). Previous studies have suggested that the first stage in the development of IP may be similar to that of an inflammatory polyp (21). Select bacterial pathogens, specifically gram negative bacteria, have been previously suggested as the initial inflammatory event as recently as 2012 American Rhinologic Society's key note speech (22). This in conjunction with lack of published literature evaluating the microbiologic flora of IP patients lead to this investigation. With an unclear aetiology for IP, our goal was to identify whether a sinonasal specific microbiologic presence may help explain IP initiation.

We compared our IP microbiology results to those of a large CRS culture result series by Kingdom et al. (8), with particular interest in the patterns of gram-negative organisms. In their study, they found gram-negative rods in 20% of total isolates, 24% of total cultures, and 34% of all patients. Compared to their study, our study demonstrated gram-negative organisms in 20% of isolates, 14% of total cultures, and 46% of patients. Thus, in terms of total number of isolates and positive cultures, it seems that

bacterial prevalence is similar in IP compared to that of CRS with no IP. There is a 12% difference in prevalence of gram-negative organisms in terms of total number of patients, but because of small sample size of the primary surgery group, significance cannot be derived from this difference. Compared to a large series of CRS bacterial pathogens, we did not identify any significant variations in microbiologic culture results.

In addition, we compared our IP microbiology results to those of a CRS cultures result series done by our institution. We collected 49 cultures on 23 cases of CRS in 2011-2012 for a total of 51 isolates. In our study, we found gram-negative organisms in 24% of isolates, 24% of cultures, and 52% of patients. Compared to the CRS culture result series of Kingdom et al, we had an increased prevalence of gram-negative organisms in terms of total number of patients. However, comparing our CRS microbiology results to the IP microbiology results shows that the bacterial prevalence is similar (52% to 46%, respectively).

There were several limitations to this study. This was a retrospective study and thus it is difficult to clearly establish the relationship between bacterial infections and inverted papilloma. Second, we included 26 IP patients to identify any trends, but a larger series would improve the power of our study, although we felt the size was adequate as an initial investigation. Finally, we used standard bacterial culture based techniques. Although this is an acceptable form of bacterial identification and utilized in our comparison groups, bacterial culture-independent microbiology has greater accuracy. Future investigation into culture-independent methods for both a series of IP and standard CRS patients may help identify any microbial differences. Future investigation may be considered with culture-independent methods.

Conclusion

The aetiology of IP remains unknown. To our knowledge, this is the first reported study that has investigated the bacteriology of inverted papilloma with the goal of identifying differences in sinonasal microbiology cultures compared to that of CRS patients. In our study, the most common bacterial isolates found in IP were SCN, *Propionibacterium*, *Staphylococcus aureus*, and *Streptococcus*. Prevalence of gram-negative organisms in IP was similar to that of CRS. Although further investigation is necessary, this pilot investigation did not identify any microbial differences that may explain the aetiology of IPs. A larger multi-centre study needs to be conducted to produce more definitive results.

Authorship contribution

LK: Design, acquisition of data, analysis and interpretation of data, drafting manuscript, final approval of draft. NC: Design of

study, revision of manuscript, final approval of draft. JP: analysis and interpretation of data, revision of manuscript, final approval of draft. DK: Design of study, revision of manuscript, final approval of draft. ZZ: analysis and interpretation of data, revision of manuscript, final approval of draft. NA: Design, revision of manuscript, final approval of draft:

Conflicts of Interest

No corporate affiliations associated with any authors in this study exist.

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