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Recurrent respiratory papillomatosis disease course in immunosuppressed populations

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Main Article

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Abstract

Objective. Recurrent respiratory papillomatosis is a benign manifestation of human papillomavirus types 6 and 11 in the respiratory tract. Disease is recurrent, and factors predicting these recurrences and severity of disease are incompletely characterised. This retrospective cohort study examined the relationship of immunosuppression with recurrent respiratory papillomatosis morbidity.

Methods. A retrospective cohort of 97 adult patients with recurrent respiratory papillomatosis treated at a tertiary referral centre from 2005 to 2020 was conducted. Measures assessed included inter-surgical interval, Voice Handicap Index ('VHI-10') and anatomical Derkay scores.

Results. Bivariate analyses comparing average inter-surgical interval, Voice Handicap Index and Derkay scores in immunosuppressed and healthy patients were insignificant. When controlling for diabetes mellitus and comparing immunosuppressed to healthy patients, inter-surgical interval and Voice Handicap Index change were insignificant ($p = 0.458$ and $p = 0.465$, respectively).

Conclusion. Recurrent respiratory papillomatosis morbidity for immunosuppressed patients did not significantly differ from that of immunocompetent patients.

Introduction

Recurrent respiratory papillomatosis is the pathological process of upper airway mucosal infection by human papillomavirus (HPV) types 6 and 11[1–3] causing growth of papillomatous disease. Papillomatous growth can cause dysphonia when the vocal folds are involved, and bulky disease can obstruct the airway. Recurrent respiratory papillomatosis is treated but not cured by surgical excision, and recurrence is common.[4] The Derkay Score is an anatomical score of tumour burden that can be used to classify the disease.[2,5] The goals of treatment are maintaining a patent airway, preserving voice quality, and balancing quality of life with a frequent need for procedures.

The burden of recurrent respiratory papillomatosis infection is significant. Recurrent respiratory papillomatosis affects thousands of people each year; an estimated 15 000 debulking procedures are performed every year in the USA, amassing over $150 million in healthcare costs.[6] Studies have linked worsened voice quality in recurrent respiratory papillomatosis patients with depression.[7,8] Additionally, recurrent respiratory papillomatosis has been associated with a lower quality of life, both in children with recurrent respiratory papillomatosis and in their parents.[9]

Treatment of recurrent respiratory papillomatosis remains primarily surgical, but the available options are evolving. Treatment in the office setting can decrease the use of general anaesthesia over time.[10–12] Adjuvant medical therapies are available for more aggressive disease. Intralesional injection of cidofovir or bevacizumab have been shown to increase the inter-surgical interval, and the quadrivalent HPV vaccine (Gardasil) has also shown value in decreasing recurrence rates and frequency of surgical intervention in patients with recurrent respiratory papillomatosis.[7,10] Such treatment is now often included in management of the disease.

Recurrence is standard in recurrent respiratory papillomatosis, and patients often seek guidance regarding expectations and factors that might predict recurrence. Factors affecting recurrence rates include juvenile-onset disease (as compared to adult-onset disease) and infection with HPV type 11.[13–15] There have also been studies on the effects of factors like laryngopharyngeal reflux and age on recurrent respiratory papillomatosis morbidity.[4,11] However, immunosuppression and diabetes mellitus have been incompletely studied within the context of recurrent respiratory papillomatosis. To our knowledge, there has not been any specific study into whether immunosuppressive states lead to a worsened course of recurrent respiratory papillomatosis. Regarding diabetes mellitus, one study analysed its relationship with recurrent respiratory papillomatosis in a retrospective cohort. The study found that diabetes mellitus as a binary factor was not

associated with a worsened recurrent respiratory papillomatosis course when examining the number of interventions, anatomical Derkay scores and presence of dysplasia.[16] However, that study included only six diabetes mellitus patients, and was one of only a few such studies.

We aimed to further elucidate the relationship between immunosuppression and recurrent respiratory papillomatosis, including a distinct analysis of diabetes mellitus patients. We performed a retrospective cohort analysis of impact on recurrent respiratory papillomatosis disease course by comparing Voice Handicap Index ('VHI-10') scores, Derkay Scores and inter-surgical interval among these patient populations.

Materials and methods

A retrospective cohort analysis was performed on patients treated for recurrent respiratory papillomatosis. This study was approved by the institutional review board at the academic centre. The single-institution study included patients aged over 18 years treated at an academic tertiary care centre with a diagnosis of recurrent respiratory papillomatosis and a minimum of 18 months of surveillance. These parameters identified 97 eligible patients treated between 2005 and 2020.

The primary objective was to compare recurrent respiratory papillomatosis morbidity, defined using inter-surgical interval, anatomical Derkay scores and Voice Handicap Index improvement, between immunosuppressed patients and healthy recurrent respiratory papillomatosis patients. Diabetics were analysed separately to compare true immunosuppression to the complete absence of it, as diabetes can suppress both innate and adaptive immunology.[17,18] Thus, diabetes mellitus had the potential to act as a confounding variable within our analysis. Diabetics were further classified as poorly controlled if they had average haemoglobin A1c of greater than 8.0 per cent or were insulin-dependent (if A1c information was not available).

The overall cohort was separated into four groups: immunosuppressed patients, diabetes mellitus patients, poorly controlled diabetes mellitus patients and healthy patients. Immunosuppression (described in Table 1) was defined as: (1) active immunosuppressant use; (2) patients with immunocompromising disease such as acquired immunodeficiency syndrome (AIDS); or (3) patients undergoing chemotherapy during the study period. Any medication or condition categorised as immunocompromising had to occur during recurrent respiratory papillomatosis surveillance. Local immunosuppression, defined as inhaled corticosteroid use during the study period, was evaluated separately.

The data collected were demographic data and recurrent respiratory papillomatosis morbidity-related data, including inter-surgical interval, Derkay scores, Voice Handicap Index and development of laryngeal cancer. The mean values were compared among the three groups. We calculated the average change in Voice Handicap Index and Derkay score for each procedural intervention when both pre-operative and post-operative scores (within four weeks before or after the procedure) were available. This allowed us to assess the short-term benefit of surgical debulking. The inter-surgical interval was the number of days between two procedures, including office-based procedures. The Voice Handicap Index scores collected at patient visits were used as a metric of symptom severity and quality of life.

Comparison between immunosuppressed and immunocompetent groups was performed with bivariate analyses using: the Wilcoxon rank sum test (for average inter-surgical interval, change in Derkay score per operation), the Welch two-sample *t*-test (Voice Handicap Index change per operation) and the chi-square test (laryngeal carcinoma development). In order to control for confounding variables, multivariable regression analyses were performed, controlling for diabetes mellitus, poorly controlled diabetes mellitus and body mass index (BMI). Linear regression models were utilised to analyse average inter-surgical interval, Voice Handicap Index change per operation and change in Derkay score per operation (log transformed). A logistic regression model was used to analyse the development of laryngeal cancer. An alpha level of 0.05 was determined. All statistical analyses were performed in R studio software, and figures were created in Microsoft Excel or R studio software.

Table 1. Immunomodulating medications and indications for immunosuppressed study population

Pt no.	Immunomodulating medication	Indication(s)
1	Rituximab, Solu-Medrol®	Neuromyelitis optica
2	Paclitaxel, gemcitabine	Pancreatic cancer
3	Sirolimus, prednisone, cyclosporine	Kidney transplant recipient
4	Rituximab, cyclophosphamide, vincristine, bendamustine	B-cell lymphoma
5	Methotrexate, prednisone	Rheumatoid arthritis
6	Mesalamine, mercaptopurine	Ulcerative colitis
7	Mesalamine, mycophenolate mofetil, cyclosporine	Liver transplant recipient
8	RT	Non-small cell lung cancer
9	Doxorubicin, cyclophosphamide, paclitaxel, RT	Invasive ductal carcinoma
10	Rituximab, Solu-Medrol	Neuromyelitis optica
11	Paclitaxel, gemcitabine	Pancreatic cancer
12	Sirolimus, prednisone, cyclosporine	Kidney transplant recipient
13	Rituximab, vincristine, cyclophosphamide, cisplatin with RT	Tongue base squamous cell carcinoma

Pt no = patient number; RT = radiation therapy

Results

Ninety-seven patients met the inclusion criteria for this study. Of these, 13 were immunosuppressed and 18 had diabetes mellitus; 10 of the latter patients had poorly controlled diabetes (A1c of more than 8 per cent or insulin-dependent). Initial analyses comparing immunosuppressed and healthy patients in terms of inter-surgical interval, Voice Handicap Index change per operation and change in Derkay score per operation all showed no significant differences (Figure 1).

Initially, bivariate statistical analyses were conducted for each measurement of morbidity, comparing immunosuppressed to immunocompetent patients. Average inter-surgical interval ($p = 0.135$), Voice Handicap Index change per operation ($p = 0.546$), change in Derkay score per operation ($p = 0.503$) and laryngeal cancer development ($p = 0.578$) all lacked statistical significance (Table 2).

In order to further discern the complex relationship between immunosuppression, diabetes mellitus and

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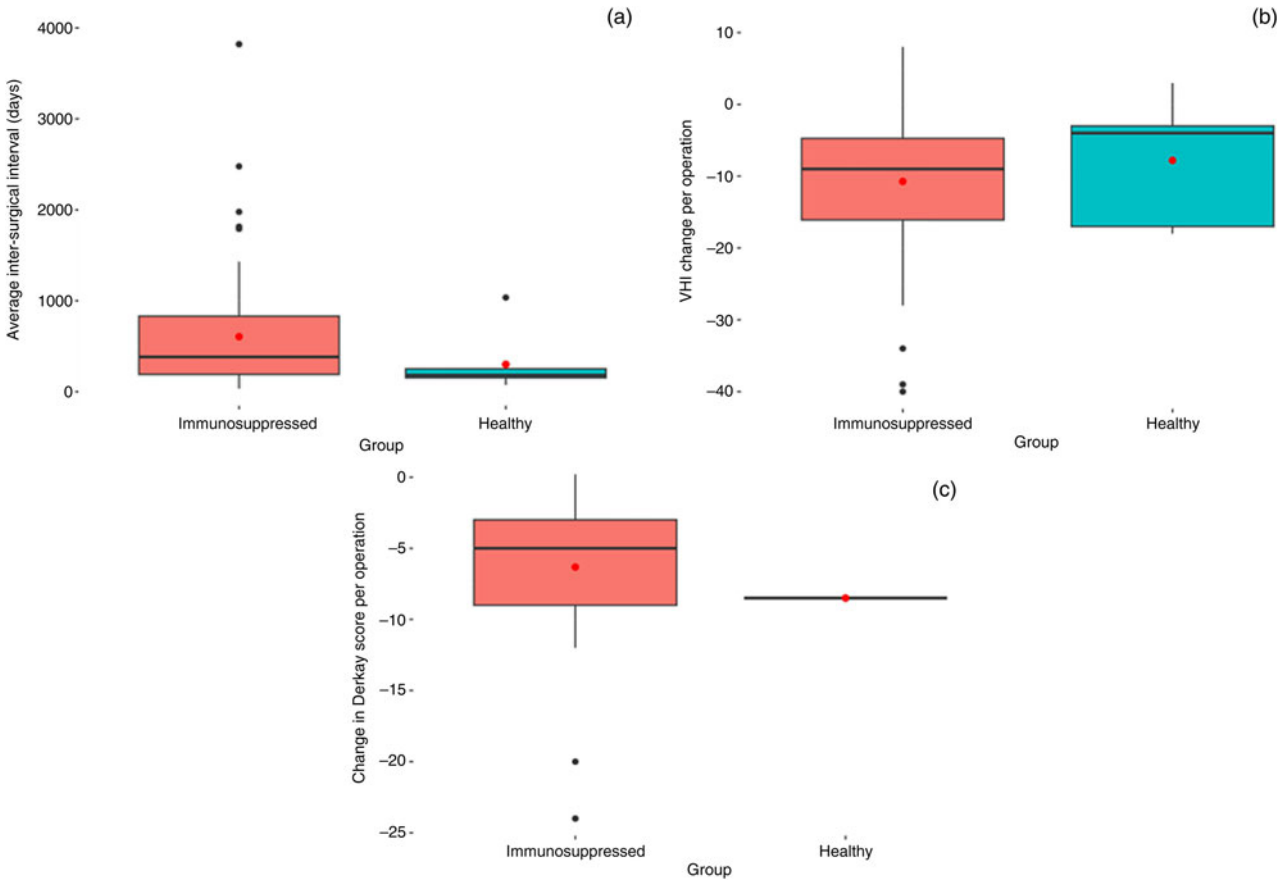

Figure 1. Comparison of immunosuppressed versus healthy patients for three measures of recurrent respiratory papillomatosis morbidity: (a) average inter-surgical interval, (b) Voice Handicap Index (VHI) change per operation, and (c) change in Derkay score per operation. No significant differences were seen between the two groups.

immunocompetence, multivariable analyses were run for each measure of morbidity. Linear regression models comparing immunosuppressed to healthy patients in terms of inter-surgical interval (estimate co-efficient = −0.346, $p = 0.458$), Voice Handicap Index change per operation (estimate co-efficient = 4.140, $p = 0.465$) and change in Derkay score per operation (estimate co-efficient = 1.251, $p = 0.566$) all lacked significance when controlling for diabetes mellitus, poorly controlled diabetes mellitus and BMI (Table 2). Immunosuppression did not significantly affect the development of laryngeal carcinoma ($p = 0.228$).

Additionally, multivariable regression models were used to examine diabetes mellitus, poorly controlled diabetes mellitus and BMI, while controlling for these factors and immunosuppression. Each of these models were conducted for average inter-surgical interval, Voice Handicap Index change per operation, change in Derkay score per operation and laryngeal cancer development (Table 3). When controlling for immunosuppression, diabetes mellitus and BMI, the poorly controlled diabetics did show more Voice Handicap Index improvement per operation than healthy patients (estimate co-efficient = 16.414, $p = 0.032$), though they did have higher average Voice Handicap Index scores initially. The remainder of these regression analyses, examining diabetes mellitus, poorly controlled diabetes mellitus and BMI, revealed insignificant findings, and, overall, BMI did not impact disease

Table 2. Bivariate and multivariable analyses of immunosuppressed versus healthy patients*

	Bivariate analysis		Multivariable analysis			
Parameter	Test type	*P*-value	Test type	Estimate co-efficient	SD	*P*-value
Average inter-surgical interval	Wilcoxon rank sum test	0.135	Linear regression model	−0.346	0.463	0.458
VHI-10 change per operation	Welch 2-sample *t*-test	0.546	Linear regression model	4.140	5.604	0.465
Change in Derkay score per operation	Wilcoxon rank sum test	0.503	Linear regression model (log transformed)	1.251	2.143	0.566
Laryngeal cancer development	Chi-square test	0.578	Logistic regression model	1.147	0.952	0.228

*Controlling for diabetes mellitus, poorly controlled diabetes mellitus and body mass index. SD = standard deviation; VHI-10 = Voice Handicap Index 10

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Table 3. Outcomes of multivariable regression models comparing morbidity of recurrent respiratory papillomatosis*

Parameter	Average inter-surgical interval	VHI-10 change per operation	Change in Derkay score per operation	Laryngeal cancer development
DM	0.155	0.815	0.858	0.769
Poorly controlled DM	0.538	0.032†	Poorly controlled DM highly correlated with DM	0.994
BMI	0.296	0.445	0.489	0.923

*In patients with diabetes mellitus, poorly controlled diabetes mellitus (DM) or elevated body mass index (BMI) compared to the healthy population, when controlling for immunosuppression, diabetes mellitus, poorly controlled diabetes mellitus and BMI. Data represent *p*-values. †Indicates significant difference. VHI-10 = Voice Handicap Index 10

Table 4. Impact of local immunosuppression on inter-surgical interval, VHI-10 change, change in Derkay score and number of recurrences

		P-values (2-sample Wilcoxon tests)		
Parameter	% (*n*) of recurrences in study population	Average inter-surgical interval	VHI-10 change per operation	Change in Derkay score per operation
Local immunosuppression	13 (13/97)	0.669	0.889	0.438

VHI-10 = Voice Handicap Index 10

burden (Table 3). Recurrent respiratory papillomatosis morbidity in patients with local immunosuppression was examined using inter-surgical interval, Derkay score and Voice Handicap Index score with two-sample Wilcoxon tests, but there were no significant differences (Table 4).

Discussion

Our analysis shows the complex relationship of immunosuppression and recurrent respiratory papillomatosis disease course. Immunosuppressed patients did not show any significant difference in terms of inter-surgical interval, change in Derkay score per operation or Voice Handicap Index change per operation. Both inter-surgical interval and Voice Handicap Index have been associated with recurrent respiratory papillomatosis morbidity.[10,11,19] These results suggest that immunosuppression may not play a role in hastening respiratory papillomatosis recurrence, as measured by inter-surgical interval, or in limiting the clinical benefits of surgical intervention, as measured by the Voice Handicap Index.

As has been shown in past literature, HPV infections are typically cleared by a robust and healthy immune response.[20] However, certain patient characteristics could theoretically lead to more significant HPV infection. For instance, chronic HPV patients tend to have a reduced level of cluster of differentiation 8 (CD8) and type 1 cluster of differentiation 4 (CD4) T cells, which are important in maintaining a strong adaptive immunity. It has been suggested that this may be because the HPV virulence factor, E6, shifts the adaptive immune response away from T-helper 1 (Th1) CD4 T cells to a T-helper 2 (Th2)-like or T-reg phenotype.[7] This change impairs the clearance of HPV infection and depresses the immune system.[7] Thus, it is imperative that immunosuppression be studied within the context of recurrent respiratory papillomatosis, to help clarify a possible relationship. While considering this immune physiology, a worsened recurrent respiratory papillomatosis disease course was expected in the immunosuppressed population, but the data in this study were not consistent with this.

Diabetes mellitus has known effects on immunity and thus possibly on recurrent respiratory papillomatosis disease course. Hyperglycaemia in general can weaken host immunity by impairing neutrophil activity and humoral immunity.[17,21] With the delayed wound healing that occurs in diabetes mellitus patients,[22] it would have been reasonable to expect a shorter inter-surgical interval or a decreased subjective benefit from surgical intervention; however, the data did not support this. Diabetes mellitus did not have an overall impact on recurrent respiratory papillomatosis disease morbidity, whether poorly controlled or not. This is in congruence with a previous study that found no relation between diabetes mellitus and a worsened recurrent respiratory papillomatosis course.[17] Our study stratified for glucose control, while the previous one did not, which further strengthens this finding. The finding that debulking led to a statistically significant higher improvement in Voice Handicap Index scores in the poorly controlled diabetes mellitus group was somewhat surprising, but possibly explained by their worse baseline Voice Handicap Index scores.

The results from this study alone should not alter counselling for immunosuppressed or diabetic patients with recurrent respiratory papillomatosis. The impact of immunosuppression on recurrent respiratory papillomatosis course may be more evident on an individual level, depending on the degree and duration of immunosuppression. These patients may be more likely to avoid or delay intervention for recurrent respiratory papillomatosis because of other healthcare concerns. Additionally, strict glucose control in diabetics is preferred when patients are undergoing any type of operation, including, but not limited to, papilloma debulking.

- Recurrent respiratory papillomatosis is a pathological process of the upper airway caused by human papillomavirus (HPV) types 6 and 11
- The burden of disease is significant, requiring repeated debulking procedures over time
- Human papillomavirus infections are typically cleared by a robust, healthy immune response; recurrent respiratory papillomatosis patients fail to clear laryngeal HPV infection
- Decreased host immune response could alter disease course, but relationship between recurrent respiratory papillomatosis morbidity and immunosuppression has not been studied
- This study showed no significant worsening of recurrent respiratory papillomatosis morbidity in immunosuppressed patients, according to inter-surgical interval and Voice Handicap Index-10
- Similarly, diabetes mellitus, even with poor glucose control, did not impact disease course, nor did local immunosuppression

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There were limitations within this study. Without a randomised cohort, there may have been a sampling bias during data collection. As a retrospective analysis, there may be bias present when interpreting results. There were a relatively low number of immunosuppressed patients ($n = 13$) and uncontrolled diabetic patients ($n = 10$), warranting caution when interpreting conclusions based on a small sample size. Finally, while diabetic patients were stratified by glucose control when A1c information was available, there were some patients without consistent primary care follow up and laboratory analysis.

This retrospective analysis of recurrent respiratory papillomatosis patients suggests that immunosuppressed patients may experience disease courses comparable to immunocompetent patients when considering the inter-surgical interval and voice quality (as measured by the Voice Handicap Index).

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Competing interests. None declared

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