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Natural Progression of Dysplasia in Adult Recurrent Respiratory Papillomatosis

Joseph E. Hall, MD¹, Karen Chen¹, Mi Jin Yoo¹, Kenneth C. Fletcher, MD¹, Robert H. Ossoff, DDS, MD¹, and C. Gaelyn Garrett, MD¹

Abstract

Objectives. Recurrent respiratory papillomatosis (RRP) is often described as a benign disease. However, the natural progression of dysplasia and transformation to squamous cell carcinoma has not been elucidated for RRP. This study delineates our extensive experience with dysplasia in RRP.

Study Design/Setting. Case series with chart review.

Subjects and Methods. Demographic data and surgical pathology were analyzed for patients diagnosed with RRP at greater than 18 years of age who underwent operative intervention without cidofovir treatment for RRP between 2004 and 2009.

Results. Fifty-four patients were identified. Dysplasia was identified in 27 of 54 patients (50%). Of the 54 patients, 50% had no dysplasia, 26% had mild dysplasia (grade 1), 11% had moderate dysplasia (grade 2), 4% had severe dysplasia (grade 3), 7% had carcinoma in situ, and 2% had squamous cell carcinoma as the highest documented degree of dysplasia. Thirty of 54 patients (55.6%) had 2 or more operative interventions. Nine of the 30 patients (30%) developed a higher dysplastic grade during the course of treatment. Time to progression averaged 16.2 ± 8.7 months for patients with initially benign disease. Of those patients with dysplasia progression, only 1 of 9 (11.1%) developed squamous cell carcinoma. Patients presenting with benign or mild dysplasia typically did not progress beyond mild dysplasia (22 of 24, 91.7%).

Conclusions. Dysplasia is common in RRP. Progression of dysplasia, especially with an initial dysplastic grading of benign or mild disease, is rare.

Keywords

RRP, dysplasia, progression, natural progression, HPV

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Recurrent respiratory papillomatosis (RRP) is often described as a benign disease with recurrent exophytic mucosal lesions (papillomas) of the respiratory tract. RRP demonstrates a bimodal distribution with peaks of incidence at 5 years of age and 20 to 30 years of age, corresponding to juvenile-onset and adult-onset RRP, respectively. Most patients develop hoarseness as their primary symptom. Human papillomavirus (HPV) 6 and 11 are the most commonly implicated etiologies in this disease, although HPV 16, 18, 31, 33, and 51 have been previously reported in patients with RRP. HPV is a small, nonenveloped DNA virus that replicates in the nucleus of host cells.

While surgical resection remains the standard of care for management of RRP, alternative treatment strategies (ie, off-label usage of intralesional cidofovir injection) are being implemented in an attempt to slow the replication of HPV and thereby decrease the amount of disease present in patients with RRP. While a recent commentary recommended a...
comparison of cidofovir with a matched series of patients, a study by Gupta et al analyzed 13 patients undergoing cidofovir treatment for RRP and concluded that intralesional cidofovir for RRP did not correlate with dysplasia progression.

Many questions remain surrounding RRP, including the natural progression of dysplasia in this disease process. This study delineates the natural progression of dysplasia in RRP via characterization of degrees of dysplasia present at operative intervention. This is the most comprehensive study to date of dysplastic change in RRP.

Materials and Methods

Vanderbilt University Medical Center (VUMC) Institutional Review Board approval was obtained. International Classification of Diseases–9 (ICD-9) codes were used to obtain the records of all patients older than 18 years at the time of diagnosis of RRP treated at the Vanderbilt Voice Center at VUMC. Patients treated at any time with cidofovir were excluded. A total of 85 patients treated for RRP from 2004 to 2009 were identified. A retrospective review of all charts was performed to obtain general patient demographic data including age, gender, date of birth, date of presentation, smoking history, and HPV subtype (if known). In addition, all operative notes were analyzed for the corresponding pathology results. Pathology reports resulted from biopsies obtained at the time of operative intervention (typically at the area of greatest disease) prior to laser ablation or microdebrider excision. In addition, when bulky disease was present, laser excision of the papilloma was performed at the base of the lesion, and the entire specimen was sent for pathologic analysis. Sufficient tissue was obtained to allow for adequate pathologic analysis at each operative intervention. Pathology results were linked with the patient, date of operation, type of operation, and HPV status. The highest degree of dysplasia at each operative intervention noted on the pathology report was recorded. Dysplasia was characterized according to standard World Health Organization classification with attention to architectural disorder, basal layer involvement, and height of mitoses. The dysplastic grading included absence of dysplasia (benign disease), mild dysplasia (grade 1), moderate dysplasia (grade 2), severe dysplasia (grade 3), carcinoma in situ, and squamous cell carcinoma (SCC). Progression of dysplasia was defined as at least 1 incremental increase in dysplastic grade. Severe dysplasia and carcinoma in situ were included as separate categories as these were distinct entities as classified by the pathologist. However, it is recognized that in some institutions, these 2 categories of dysplasia are synonymous. Most patients underwent CO2 laser vaporization/laser excision of RRP, but some underwent resection with microdebrider.

Analysis of the data was then performed. Patient demographic data were analyzed, and associations of variables with dysplasia and progression of dysplasia were made. Continuous variables were summarized in terms of percentiles and mean values ±1 standard deviation. Categorical variables were summarized in terms of frequencies and percentages. Nonparametric Wilcoxon rank-sum tests and Pearson χ2 tests (without a continuity correction) were used to test for associations with dysplasia and progression of dysplasia. P values <.05 were considered statistically significant.

Results

Eighty-five adult patients were identified. Twenty-four of the 85 patients received cidofovir and were excluded. Seven records did not have pathology results available and were thus dismissed from the study. Therefore, 54 patients had available pathology reports and no history of cidofovir use during the course of treatment. Thirty-six of the 54 patients (67%) were male, and 21 of the 54 patients (39%) had a history of smoking. The average age at first symptom of RRP was 38 years, and the average age at presentation to VUMC was 48.4 years.

The number of operative interventions for all patients ranged from 1 to 19. The time between operations for those who had more than 1 operation ranged from 23 days to 991 days. The median number of days between operations was 139.5. The average length of follow-up in this study was 11.6 years, with 43 of 54 (80%) current, 10 of 54 (19%) lost to follow-up, and 1 of 54 (2%) deceased.

Twenty-four of the 54 patients (44.4%) had HPV subtypes. Nineteen of the 24 patients were HPV 6 (79%), 3 of 24 were HPV 11 (12%), 1 of 24 was HPV 31 (4%), and 1 of 24 was HPV 59 (4%). Thirteen of the 19 patients (68%) with subtype HPV 6 presented as benign, while 8 of the 19 (42%) had dysplasia at any time during treatment. Two of the 5 patients (40%) with subtype HPV 11, 31, or 59 presented as benign, whereas 3 of the 5 patients (60%) had dysplasia at any time during treatment.

Thirty-one of the 54 patients (57%) presented with benign disease. Mild dysplasia was most common for those patients who did not present with benign disease (12 of 23, 52%) followed by moderate dysplasia (7 of 23, 30%), severe dysplasia (2 of 23, 9%), and carcinoma in situ (2 of 23, 9%). Twenty-seven of the 54 patients (50%) had dysplasia at any time during the course of treatment. Thirty patients (30 of 54, 55.6%) had 2 or more operative interventions and were used to analyze progression of dysplasia. Nine patients (9 of 30, 30%) developed a higher dysplastic grade during the course of treatment.

Thirteen of 17 patients (76%) who presented with benign disease and had 2 or more operations did not have dysplasia greater than benign disease during the course of treatment. In addition, 6 of 7 patients (85.7%) who presented with mild dysplasia and had 2 or more operations did not have dysplasia greater than mild disease during the course of treatment. Thus, 19 of 24 patients (79.2%) who presented with benign disease or mild dysplasia with 2 or more operations stayed at or below that same level of dysplasia. When considering all patients who presented with benign or mild disease with 2 or more operations, 22 of 24 patients (91.7%) did not progress beyond mild dysplasia.

When considering all patients with dysplasia (n = 27), no associations were found between gender, number of operations, or HPV subtype. Older current age was found to be associated with dysplasia at a statistically significant level.
(\(P = .009\)). History of smoking was found to negatively correlate with dysplasia at a nearly statistically significant level (\(P = .051\); Table 1).

The lowest and highest pathology results during the course of treatment were analyzed. Thirty-eight of 54 patients (70%) had benign disease as their lowest pathology result, whereas 27 of 54 patients (50%) had benign disease as their highest pathology result identified. Nine of 54 patients (16.7%) developed a higher dysplastic grade during their treatment course. When considering only the 30 patients with 2 or more operative interventions, 30% (9 of 30) developed progression of dysplasia during the course of treatment. One of the 54 patients (2%) developed SCC. This patient had a history of smoking and had a lowest grade pathology result of severe dysplasia.

Time to progression (for patients with 2 or more operative interventions) from benign disease was 16.2 ± 8.7 months, and time to progression from mild disease was 12.46 ± 5.04 months.

Seventeen patients had dysplasia and 2 or more operative interventions. Four of these patients presented as benign, 7 patients presented with mild dysplasia, and 6 patients presented with higher than mild dysplasia. Of the 4 patients who presented with benign dysplasia, 2 patients progressed to mild dysplasia with regression back to benign disease, 1 patient progressed to mild dysplasia, and 1 patient progressed from benign to mild to severe dysplasia. Figure 1 displays the dysplastic changes for these 4 patients.

Of the 7 patients who presented with mild dysplasia, 2 patients remained with mild dysplasia, 4 patients presented with mild disease and regressed to benign disease, and 1 patient transitioned from mild dysplasia to benign dysplasia 6 times before transitioning to moderate dysplasia to mild dysplasia to carcinoma in situ to moderate dysplasia. Figure 2 displays the dysplastic changes for these 7 patients.

Of the 6 patients who presented with higher than mild dysplasia, 1 patient regressed from moderate dysplasia to mild dysplasia to benign dysplasia, 1 patient regressed from severe to mild dysplasia, 1 patient transitioned from moderate dysplasia to mild dysplasia to moderate dysplasia to benign disease, 1 patient progressed from moderate dysplasia to severe dysplasia to carcinoma in situ, 1 patient progressed from severe dysplasia to SCC, and the final patient transitioned

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**Table 1. Associations With Dysplasia**

<table>
<thead>
<tr>
<th></th>
<th>No (n = 27)</th>
<th>Yes (n = 27)</th>
<th>PValue</th>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>78% (21/27)</td>
<td>56% (15/27)</td>
<td>.083</td>
</tr>
<tr>
<td>Number of operations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>52% (14/27)</td>
<td>37% (10/27)</td>
<td>.273</td>
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<tr>
<td>&gt;1</td>
<td>48% (13/27)</td>
<td>63% (17/27)</td>
<td></td>
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<td>Current age, y</td>
<td>43.9 ± 15.1</td>
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<td>.009</td>
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<tr>
<td>History of smoking</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>52% (14/27)</td>
<td>26% (7/27)</td>
<td>.051</td>
</tr>
<tr>
<td>HPV subtype</td>
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<td></td>
<td></td>
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<tr>
<td>6</td>
<td>85% (11/13)</td>
<td>73% (8/11)</td>
<td>.475</td>
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<tr>
<td>11, 31, or 59</td>
<td>15% (2/13)</td>
<td>27% (3/11)</td>
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</table>

---

**Table 2. Associations With Progression of Dysplasia From Benign Disease**

<table>
<thead>
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<td></td>
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<tr>
<td>Male</td>
<td>38% (3/8)</td>
<td>56% (5/9)</td>
<td>.457</td>
</tr>
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<td>Current age, y</td>
<td>57.88 ± 9.96</td>
<td>56.78 ± 12.36</td>
<td>.678</td>
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<tr>
<td>History of smoking</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>0% (0/8)</td>
<td>33% (3/9)</td>
<td>.072</td>
</tr>
<tr>
<td>HPV subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>75% (3/4)</td>
<td>80% (4/5)</td>
<td>.858</td>
</tr>
<tr>
<td>11, 31, or 59</td>
<td>25% (1/4)</td>
<td>20% (1/5)</td>
<td></td>
</tr>
</tbody>
</table>
from carcinoma in situ to severe dysplasia to mild dysplasia to carcinoma in situ. Figure 3 displays the dysplastic changes for these 6 patients.

**Discussion**

Despite the documented dysplastic and malignant transformation in RRP, the natural progression of dysplasia in RRP has yet to be fully elucidated. A recent study by Blumin et al\(^8\) looked at adult patients with RRP and risk factors associated with the presence of dysplasia in this disease. Their study concluded that dysplasia (without grading of dysplasia) was present in approximately 21.9% of their cohort of 73 adult patients. No associations were found with the patient risk factors studied (age, gender, tobacco history, and operative frequency) and incidence of dysplasia, however.\(^8\)

While discordance in grading dysplasia among pathologists has been noted to be high,\(^9\) the World Health Organization recommends continuing reporting dysplasia in RRP, and this remains one of our primary markers for evaluating the future dysplastic and malignant potential for this disease process.\(^6,10\)

As the study by Blumin et al looked at dysplasia versus no dysplasia in their cohort without analysis of dysplastic grades, a commentary in that same issue promoted the use of grading of dysplasia in RRP as it is likely that the degree of dysplasia can predict biological behavior.\(^6,8\) Further support for the necessity of analyzing grades of dysplasia in RRP comes from a study by Lee et al\(^3\) in which a high incidence of malignant transformation was noted in Taiwanese patients with RRP.

In accordance with the recommendations above, we analyzed the natural progression of dysplasia in RRP. Patients treated with cidofovir (n = 24) at any time during the course of treatment were excluded given the confounding impact that cidofovir would have had on our analyses.

Based on the results outlined in the present study, 50% (27 of 54) of patients with RRP had dysplasia. While dysplasia is common in RRP, only 9 of 30 patients (30%) with RRP and 2 or more operative interventions developed a higher dysplastic grade over time. The time to progression averaged 16.2 ± 8.7 months for patients with initially benign disease. Older current age was the only variable determined to be associated with dysplasia at a statistically significant level. This association could be related to the fact that older patients have had more time for dysplastic changes to occur. Progression of dysplasia from benign or mild disease was not associated with gender, current age, smoking, or HPV subtype at a statistically significant level. Our results demonstrating no statistically significant associations between dysplasia and progression of dysplasia and gender or history of smoking agree with previous studies on risk factors for dysplasia in RRP.\(^8\) While HPV 6 was the most common subtype found in our cohort, no conclusions regarding HPV status and dysplasia or progression of dysplasia were able to be made with this analysis due to the limited numbers of patients with documented HPV subtypes.

 Patients presenting with benign or mild dysplasia typically did not progress beyond mild dysplasia (22 of 24 patients, 91.7%). This finding may be influenced by the fact that the appearance of benign and early dysplasia in RRP is similar. Regardless, this high number indicates that patients who

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**Table 3. Associations With Progression of Dysplasia From Mild Disease**

<table>
<thead>
<tr>
<th>Progression of Dysplasia</th>
<th>No (n = 11)</th>
<th>Yes (n = 6)</th>
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</thead>
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<td>Gender</td>
<td></td>
<td></td>
<td>.858</td>
</tr>
<tr>
<td>Male</td>
<td>45% (5/11)</td>
<td>50% (3/6)</td>
<td></td>
</tr>
<tr>
<td>Current age, y</td>
<td>56.64 ± 8.71</td>
<td>58.5 ± 15.16</td>
<td>.773</td>
</tr>
<tr>
<td>History of smoking</td>
<td></td>
<td></td>
<td>.21</td>
</tr>
<tr>
<td>Yes</td>
<td>9% (1/11)</td>
<td>33% (2/6)</td>
<td></td>
</tr>
<tr>
<td>HPV subtype</td>
<td></td>
<td></td>
<td>.571</td>
</tr>
<tr>
<td>6</td>
<td>83% (5/6)</td>
<td>67% (2/3)</td>
<td></td>
</tr>
<tr>
<td>11, 31, or 59</td>
<td>17% (1/6)</td>
<td>33% (1/3)</td>
<td></td>
</tr>
</tbody>
</table>

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**Figure 2. Pathology results and dysplasia progression for 7 patients who presented with mild dysplasia. CIS, carcinoma in situ; SCC, squamous cell carcinoma.**

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**Figure 1. Pathology results and dysplasia progression for 4 patients who presented with benign dysplasia. CIS, carcinoma in situ; SCC, squamous cell carcinoma.**

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Dysplasia is common in RRP. While most patients, especially those with an initial dysplastic grading of benign or mild disease, do not progress, dysplasia in adult RRP is significant and monitoring of pathology at each operative intervention is imperative.

Conclusions
This study delineates the natural progression of dysplasia in RRP by characterizing the degrees of dysplasia over time. Dysplasia is common in RRP. While most patients, especially those with an initial dysplastic grading of benign or mild disease, do not progress, dysplasia in adult RRP is significant and monitoring of pathology at each operative intervention is imperative.

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Author Contributions
Joseph E. Hall, conception and design, creation of database, institutional review board (IRB) application, data acquisition, data analysis, drafting and editing manuscript, final approval; Karen Chen, data collection, IRB application, drafting and revising manuscript, final approval; Mi Jin Yoo, data collection, figure design, drafting/revising manuscript, final approval; Kenneth C. Fletcher, conception of study, revision of manuscript, final approval of the version to be published; Robert H. Ossoff, conception and design of study, revision of manuscript, final approval; C. Gaelyn Garrett, conception and design of study, drafting and revision of manuscript, final approval.

Disclosures
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