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Laryngoscopic Distribution of Adult-Onset Recurrent Respiratory Papillomatosis: A Longitudinal Study

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Objectives/Hypothesis: To describe recurrence patterns in patients with recurrent respiratory papillomatosis (RRP) following surgical intervention.

Study Design: Single-center, retrospective, longitudinal case series.

Methods: Initial and follow-up laryngoscopic examinations of seven previously untreated adult-onset RRP patients were reviewed. Patients were followed longitudinally for periods ranging from 3 months to 7 years. Lesion locations were recorded using a twenty-one region laryngeal schematic, and maps were generated to illustrate the distribution of disease before and after cold-knife or potassium-titanyl-phosphate laser intervention. Univariate and multivariate analyses were employed to examine variables affecting recurrence patterns.

Results: Across all patients, a statistically significant correlation between initial distribution and primary recurrence was observed. Seventy-five percent of new lesions were adjacent to regions with preexisting disease; 83% of new glottic lesions were adjacent to preexisting glottic lesions, and 66% of supraglottic lesions were adjacent to preexisting supraglottic regions. No statistically significant differences in recurrence rate were observed across sites.

Conclusions: In previously untreated patients with adult-onset recurrent respiratory papillomatosis, lesions tended to recur either in the same regions or regions adjacent to those affected at the time of initial surgery.

Key Words: Recurrent respiratory papillomatosis, voice, recurrence, vocal fold, human papillomavirus.

Level of Evidence: 4

INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a rare, chronic disease caused by human papillomavirus (HPV) and characterized by exophytic papillomatous lesions of the respiratory tract, particularly the larynx.1 Adult-onset RRP has an estimated incidence of 1.8 per 100,000 patients.2 Those affected by the disease often require multiple interventions with prolonged clinical courses complicated by frequent recurrence, decreased voice-related quality of life, and in rare cases, airway compromise.3,4 Additionally, persistent RRP is linked to malignant transformation.5,6 Given the severity and morbidity of this disease, investigation regarding the natural history and recurrence patterns in patients with RRP are critical to our increased understanding of the disease. These data also provide a platform for enhanced patient counseling. In the current study, we sought to provide insight regarding recurrence patterns employing a novel laryngeal schematic previously described by our group.7

A number of previous studies have examined the anatomic distribution of RRP lesions within the larynx.1,3,8,9 Previously, our group described the distribution of RRP lesions in untreated patients using a novel 21-region laryngeal schematic7 to provide insight into the laryngeal distribution of RRP lesions free from the influence of therapeutic intervention. Employing this schematic, our group sought to study patients longitudinally to assess lesion recurrence patterns. Interestingly, few studies have analyzed recurrence patterns over time, and most studies fail to provide information regarding initial disease presentation as a comparator for post-treatment recurrence. Kim and Baizhumanova described recurrence patterns after surgery for RRP across 10 anatomical subsites and found that the anterior commissure, subglottis, and epiglottis were the most common sites of recurrence.10 However, this study used highly aggressive therapy involving microlaryngeal surgery that included demucosalization of the surrounding larynx, 585-nm pulsed-dye laser, and intralesional cidofovir injection. Thus, it may not be representative of the vast majority of RRP patients. Additionally, that work did not compare the impact of treatment to disease distribution at diagnosis, making it difficult to discern actual treatment effects.

The standard of care for RRP treatment is ablation, primarily microdebridment and potassium-titanyl-phosphate (KTP) laser therapy. The effect of treatment on recurrence of...
RRP is unknown, lending itself to the generation of several hypotheses. Conceivably, lesions may persist in laryngeal regions that are difficult to access during treatment, as proposed by Derkay and Wiatrak. Iatrogenic squamous metaplasia may also play a role in recurrence patterns by generating epithelial transition zones for which HPV has a predilection. Additionally, recurrence may occur in regions naturally more conducive to postprocedural HPV survival or in regions of normal epithelial cells harboring latent HPV.

Other influences may include the pattern and extent of initial disease, the presence of disease in adjacent regions, or even individual loquaciousness.

The current study aimed to longitudinally describe the anatomic distribution of laryngeal RRP in a previously untreated cohort through treatment with microlaryngeal surgery and/or KTP therapy. To analyze the anatomic distribution of lesions, we employed our previously reported 21-region laryngeal schematic, as it provides enhanced resolution compared to previously described laryngeal diagrams. Ultimately, we sought to provide additional insight regarding recurrence sites as a means to improve our collective understanding of this challenging and unpredictable disease.

MATERIALS AND METHODS

Subjects

The current study was approved by the institutional review board at the New York University School of Medicine. This single-center, single-surgeon study involved retrospective chart review of previously untreated patients who were newly diagnosed with adult-onset RRP between 2008 and 2018. All patients received operative treatment from a single surgeon and follow-up therapy with a KTP laser. Patients who were diagnosed at other institutions, had history of previous treatment, or who lacked KTP laser ablation were excluded. Patients with juvenile onset RRP (diagnosed prior to 16 years of age) were also excluded. Seven patients met criteria for this study with high-quality laryngoscope examination videos. Patient demographics and self-rated loquaciousness were also collected.

Data Collection

The initial and all follow-up laryngoscopic examinations were reviewed. Data regarding disease distribution were recorded for each of the 21 laryngeal regions before and after each intervention. Patients were followed for periods ranging from 3 months to 7 years, depending on interval between follow-up dates. All patients received a preoperative examination followed by prompt treatment in the operating room for in-depth exam and complete resection of all visualized disease. All patients received a 1-month postoperative examination. Further examinations and KTP laser therapy varied based on individual recurrence rates and symptoms for each patient.

Schematic Generation

Raw data collected from laryngoscopic examination videos were analyzed using Tableau 10.5 (Tableau Software, Seattle, WA) to create graphic representations of the laryngeal distribution of RRP. The schematic contained 21 regions as described previously. The anatomic correlates of the schematic are shown in Figure 1. Schematics were color-coded, with regions containing RRP lesions black and regions free from disease white. Heat maps were also generated to illustrate regions of most frequent recurrence from no recurrence in white to most frequent recurrence in red.

Statistical Analysis

Each region of the schematic was counted as a separate data point for each of the seven patients. A Mann-Whitney test was employed to compare true vocal fold regions to aryepiglottic regions. Cochran-Mantel-Haenszel statistics assessed the association between recurrent and preoperative disease across all regions. Correlations between self-rated loquaciousness, recurrence rate, and time between follow-ups were compared using univariate analysis. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). All P values reported were two-sided; statistical significance was defined as P < .05.

RESULTS

Demographics

Seven patients were included in this study. At the time of diagnosis, patient age ranged from 32 to 58 years,
with a mean of 44.4 years. Five patients (71.4%) were male and two (28.6%) were female. Three patients (42.9%) were former smokers and four (57.2%) reported no history of smoking tobacco. Two patients (28.6%) reported rare to no alcohol use, two reported alcohol use several times per month (28.6%), and three patients reported alcohol use several times per week (42.9%). On the seven-point talkativeness scale, patients ranged in level of self-reported loquaciousness from 4.5 to 6.19, with an average of 5.05. The cohort underwent between one

Fig. 2. Heat maps of the distribution of recurrent respiratory papillomatosis lesions. Colors are scaled to show most frequent sites of recurrence for individual patients. Laryngeal schematics are black for regions affected by disease and white for unaffected regions. Scalpel symbols mark when patients went to the operating room for cold-knife excision, and laser burst symbols mark when patients received potassium-titanyl-phosphate laser therapy. Up to the fifth postoperative examination is shown for each patient.
and four KTP treatments following initial surgery, with a mean of 2.0 KTP treatments during the study period.

**Overall Recurrence Patterns**

The distribution of RRP lesions for each patient over time is shown in Figure 2. Across all regions for all patients, 74.5% of recurrent disease occurred in regions that were involved prior to treatment. Overall, recurrence of disease occurred in 88.4% of regions involved by RRP at presentation. A region-by-region Cochran-Mantel-Haenszel comparison of preoperative and primary postoperative disease distribution demonstrated positive correlation ($P = .0004$). Over the study period across all patients, 12 new lesions were noted in regions that were not previously affected by initial disease. Of these lesions, 50% occurred on the true vocal folds and 50% were supraglottic. One subglottic lesion was noted in this cohort. Seventy-five percent of new lesions were adjacent to regions with preexisting disease. Of the new lesions, 83% of glottic lesions were adjacent to preexisting glottic lesions, and 66% of supraglottic lesions were adjacent to preexisting supraglottic lesions.

**Recurrence Rates**

Of the seven patients included in this study, 71.4% recurred in one or more true vocal fold regions at 1 month, and 50% recurred in aryepiglottic regions during this time interval. Across individual regions, the average 1-month recurrence rate for true vocal fold regions was 45% compared to aryepiglottic regions at 23%. Due to the small sample size, the difference between these recurrence rates did not achieve statistical significance ($P = .2356$). The average proportion of true fold regions with recurrence at 1 month was 38% compared to 19% in aryepiglottic regions ($P = .2914$). Of the patients with recurrence in aryepiglottic regions at 1 month, 100% recurred in ipsilateral true vocal fold regions.

**Effect of Self-Rated Loquaciousness**

Linear regression compared patient self-rated loquaciousness to percent recurrence at 1 month; no significant relationship was observed ($R^2 = 0.011$, $P = .8228$). Similarly, no relationship was observed between loquaciousness and interval between treatments ($R^2 = 0.0406$, $P = .6648$).

**DISCUSSION**

Given the chronic and recurrent nature of RRP, insight regarding the longitudinal distribution and response to intervention is likely of critical importance, particularly with regard to patient counseling and managing their expectations for recurrence. Many studies focused on various treatment options, including microlaryngeal surgery, KTP laser, pulsed-dye laser, and antiviral therapies. However, studies focusing on longitudinal recurrence patterns of RRP are scarce. Just one study investigated the direct impact of surgical intervention on distribution of RRP, and none compared recurrent disease to distribution at diagnosis. The current study sought to elucidate the longitudinal distribution of RRP after ablative intervention and the putative factors that may impact distribution and rate of recurrent disease. This study is the first to include a previously untreated cohort to provide detailed longitudinal information about RRP distribution.

Cohort analysis revealed that 88.4% of regions affected by disease at diagnosis recurred after excisional treatment. A statistically significant correlation was observed between regions with preoperative disease and regions in which patients experienced primary recurrence at 1 month. These findings align with prior studies suggesting a tendency for HPV to remain in mucosa as a latent infection following ablative therapy. Similarly, other studies suggested that patients requiring multiple RRP excisions may have breakdown of the basement membrane, allowing deeper invasion of the virus and decreasing the likelihood of microscopic disease excision.

Abramson et al. previously hypothesized that latent viral presence may be responsible for RRP recurrence, but a detailed longitudinal analysis of recurrence patterns has never been presented. Due to the homogeneity of the anatomic distribution of RRP lesions throughout the course of treatment in the current cohort, our findings implicate durable, latent virus as a likely cause of recurrence. These data also demonstrate that when disease develops in new anatomic areas, these new regions are likely to be adjacent to those regions in which disease was originally found, which is highly suggestive that latent virus may play a critical role in recurrence patterns of RRP and could serve as the agent for disease spread between regions.

Other explanations for the phenomena observed in this study do, however, exist. For instance, it is possible that rather than latent disease, incomplete ablation of existing RRP lesions lead to recurrence in similar anatomic areas. Although the current cohort tended to have accessible disease on the true vocal fold, in other cases, it is possible that some regions of the larynx may be difficult to access or visualize, causing persistence and continued spread of infection.

In addition to recurrence patterns, our study also examined recurrence rates across all patients; every patient had a 1-month postoperative examination as a standardized time point for recurrence rate. No statistically significant differences in recurrence rates between glottic and supraglottic regions were observed despite comparatively higher glottic recurrence at 1 month postoperation. Variability in recurrence rates between glottic and nonglottic regions may exist given the differences between these regions with regard to both structure and exposure to mechanical trauma (e.g., phonotrauma). The limited sample size posed an obstacle to further exploration of these issues.

The current study also examined the effects of self-rated loquaciousness on treatment outcomes. The underlying hypothesis was that patients who are more loquacious may generate more trauma to the vocal fold tissue, which could potentiate the spread and recurrence of RRP, as has been hypothesized as the reason for lesion predilection for the mucosal vocal folds. Bastian et al. found that mucosal lesions of the larynx were strongly associated with high self-rated talkativeness. However, linear regression...
analysis of our cohort revealed no significant correlations between self-rated loquaciousness and recurrence at 1 month or average months between follow-up appointments. Again, the limited sample size may fail to detect these relationships, and a larger-scale prospective study is likely to yield improved insight.

The current study is not without limitation. As a retrospective analysis with a relatively small sample size, this study is qualitative and descriptive. Specific information regarding the treatment of individual lesions is limited; for example, the level of excision achieved for each lesion was not recorded. Additionally, this cohort was drawn from a single academic voice center, and therefore, the potential for bias toward patients with symptomatic voice complaints likely prevailed. Finally, genotyping of these lesions could provide additional correlative insight regarding disease recurrence rate and pattern. Certainly, HPV type warrants consideration in future investigation. In spite of these shortcomings, these data are the first in-depth, qualitative examination of recurrence patterns in patients with RRP using a highly detailed laryngeal schematic. Both the concept and the schematic are likely critical to future larger scale studies focusing on broader patterns of RRP recurrence and possible predictive factors to guide treatment of this chronic disease.

CONCLUSION

RRP lesions tended to recur either in the same regions affected at the time of diagnosis or in regions adjacent to those affected at the time of diagnosis. No statistically significant differences in recurrence rates were observed between individual regions of the larynx. In addition, no significant correlations were observed between self-rated loquaciousness and disease recurrence at 1 month following definitive surgical resection. These data offer qualitative analysis of recurrence patterns in RRP, and will hopefully serve as a foundation for future large-scale investigation.

BIBLIOGRAPHY