Inhaled Triamcinolone With Proton Pump Inhibitor for Treatment of Vocal Process Granulomas: A Series of 67 Granulomas

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Objectives: We sought to analyze the outcomes of vocal process granulomas treated with proton pump inhibitors and inhaled triamcinolone acetonide.

Methods: We reviewed the medical records of patients with a diagnosis of contact granuloma or vocal process granuloma between 1995 and 2008. Data included age, gender, intubation history, reflux history, lesion location, previous treatment methods, treatment course, and recurrence. All patients were treated with daily or twice-daily proton pump inhibitors and inhaled triamcinolone acetonide (300 µg 3 times a day).

Results: Sixty-seven granulomas were diagnosed in 54 patients: 13 bilateral and 41 unilateral. Twenty patients, including all 11 women, had a recent history of intubation. Sixty-two granulomas in 50 patients were treated with triamcinolone and a proton pump inhibitor. Of the 57 granulomas that completed treatment, 5 (9%) did not respond (mean follow-up, 50 weeks; range, 30.3 to 78.3 weeks), 13 (22%) partially responded (mean follow-up, 11 weeks; range, 3 to 30 weeks), and 40 (69%) completely responded (mean follow-up, 21 weeks; range, 5.9 to 84.6 weeks). Three cases had recurrence: 2 nonresponders and 1 complete responder. One patient developed oral thrush.

Conclusions: In this study, vocal process granulomas occurred more frequently in men, whereas women developed granulomas only after intubation. The anti-inflammatory action of inhaled triamcinolone combined with antireflux proton pump inhibitors successfully treats most vocal process granulomas with low rates of side effects and recurrence.

Key Words: gastroesophageal reflux, hyperfunctional voice abuse, inhaled steroid, proton pump inhibitor, speech therapy, vocal process granuloma.

INTRODUCTION

Vocal process granulomas of the larynx are relatively uncommon benign lesions emanating over the vocal process. Common synonyms include contact granuloma, laryngeal granuloma, and pyogenic granuloma, among others, with vocal process granuloma gaining favor as an inclusive term identifying the anatomic location in contrast to more narrowly defined pathophysiologic or etiologic descriptions. Vocal process granulomas are commonly associated with laryngopharyngeal reflux disease, intubation trauma, and vocal abuse. However, traditional therapy with antireflux regimens, voice therapy, and/or surgical excision has demonstrated variable success.

Chevalier Jackson was the first to report "contact ulcers" along the posterior glottis in 1928. With his son, Chevalier L. Jackson, Jackson surmised the mechanical action of abusive phonation as an etiologic mechanism and recognized that men were more commonly affected. Other etiologic factors were identified, including direct trauma from intubation injury leading to a granuloma in a woman in 1932. New and Devine substantiated this finding with a larger case series of 9 postintubation contact ulcer granulomas. In 1968, Cherry and Margulies published a report using an acid-barium swallow study to associate gastroesophageal reflux with granuloma formation. Delahunty and Cherry corroborated their clinical suspicion in the laboratory by demonstrating granuloma formation in dogs whose larynges were exposed to acid, compared with no granuloma formation in controls. Subsequent clinical studies supported the effect of reflux in the pathogenesis of vocal process granuloma. In a small study comparing 26 patients with contact granuloma with 19 healthy controls, Ylitalo and Ramel demonstrated that pharyngeal reflux events were significantly more common in the experiment-
Identification of causal factors is important in the treatment of vocal process granulomas. Treatment options include voice therapy, antireflux therapy, surgical removal, botulinum toxin injections, and steroid therapy. Although voice therapy is useful in the management of vocal process granuloma, disagreement remains regarding its timing, method, and effectiveness. Peacher and Holinger reported success with vocal reeducation in contrast to voice rest. Similarly, Bloch et al. reported a 71% success rate in the use of conventional voice therapy for disease resolution. However, Ward et al. suggested that the effectiveness of voice therapy was secondary to that of antireflux therapy, which was emphasized as the most important treatment method. Aggressive antireflux management of laryngeal granulomas is a well-documented approach. In 1999, Roh et al. reported success with topical inhaled steroids as the principal therapy for vocal process granuloma. Although surgical intervention represents a treatment option, it is associated with a high rate of recurrence and is generally indicated for airway obstruction, diagnostic biopsy, and granulomas that are nonresponsive to conservative management. Perioperative steroid injection and postoperative systemic corticosteroids have been proposed as adjuvant therapy. Additionally, botulinum toxin injections are a more recent treatment option that has been shown to aid the resolution of vocal process granuloma in poor surgical candidates whose cases were unresponsive to conservative medical management.

Despite the spectrum of management strategies, vocal process granulomas continue to be difficult to eradicate and demonstrate a propensity for rapid return. Although management strategies have been proposed, a universally accepted approach to managing granulomas is lacking. Since the 1999 publication of Roh et al. on the success of inhaled budesonide for contact granuloma, topical steroid therapy has not been mentioned in the literature as a treatment regimen. The purpose of this investigation was to analyze the effectiveness of the combination of inhaled triamcinolone acetonide and proton pump inhibitors (PPIs) in the treatment of vocal process granuloma. In this case series, the success of the combination medical therapy was measured by partial and complete resolution of the granulomas, as well as by medical failure that required surgical excision.

**METHODS**

The medical records of patients with a diagnosis of contact granuloma or vocal process granuloma were reviewed at a tertiary care medical center between 1995 and 2008. The retrospective review of patient records was exempted by the Johns Hopkins Medicine Institutional Review Board (JHM-IRB X 04-06-25-01e). The diagnosis was made by rigid or flexible videostrobolaryngoscopy in an outpatient clinic setting. Data collected included age, gender, occupation, intubation history, history of gastroesophageal or laryngopharyngeal reflux symptoms or signs, lesion location, previous treatment methods, treatment course, and recurrence.

After diagnosis, all patients were treated with a PPI either daily or twice daily and with inhaled triamcinolone acetonide (300 μg 3 times a day). Patients were started on a 6- to 8-week trial, with further medical therapy based on repeat examination and videostrobolaryngoscopy. Follow-up evaluations took place every 6 to 12 weeks until recovery. Failure of treatment was defined as no improvement in signs or symptoms following 2 courses of therapy. Time to partial recovery, time to complete recovery, and time of treatment were measured in weeks. Recurrences and contralateral lesions that formed during the treatment trial were recorded. Other treatment methods, including voice therapy, botulinum toxin injection, steroid injection, and systemic steroid treatment, were also recorded. Patients in whom medical therapy failed, who needed a biopsy, or who had an obstructive granuloma were advised to undergo surgery.

Completion of treatment was defined as completion of at least one 6- to 8-week course of medical therapy with follow-up. Resolution of vocal process granulomas was determined by modification of the grading system of Emami et al. Cases with complete resolution of symptoms and no identifiable lesion were defined as “completely resolved.” Cases with discoloration, including erythema, without a lesion were defined as “completely resolved.” Cases that had improvement in symptoms, as well as a reduction in the size of the granuloma, and any lingering lesion, including ulceration, were defined as “partially resolved.” Cases that demonstrated no symptomatic improvement or a worsening of symptoms were defined as “nonresponsive” to treatment.

Statistical analyses were performed with MedCalc 3000 (Foundation Internet Services, Pittsburgh, Pennsylvania). We applied a χ² test to the location of unilateral lesions, the association of intubation trauma with gender, and the association of vocal abuse with gender. Values for p were determined with χ² tests; values less than 0.05 were considered significant.

**RESULTS**

Overall, 67 granulomas were diagnosed in 54
patients. Forty-three men and 11 women were included, with an average age of 54.4 years and an average follow-up of 45.9 weeks (range, 3 to 362.7 weeks). Seven patients were professional voice users. Forty-one patients had unilateral lesions (76%), and 13 patients had bilateral disease (24%). A contralateral granuloma in 4 patients developed after initiation of therapy for the principal lesion. Of patients with unilateral vocal process granulomas, 32 (78%) had left-sided and 9 (22%) had right-sided lesions (p < 0.001). One patient was noted to have a contralateral ulcer that did not develop into a granuloma. Twenty patients, including all 11 women, had a recent history of intubation. Intubation trauma was associated with granuloma formation in men (p < 0.001). The frequencies of presenting symptoms are presented in the Table.

Twenty-seven patients had previously been treated with PPIs alone, either daily or twice daily, and had not completely responded. Seventeen patients previously underwent surgery (12 had more than 1 procedure) with recurrence of the vocal process granuloma. Other previous treatment included voice therapy in 1 patient, inhaled steroids in 3 patients, systemic steroids in 5 patients, steroid injection in 1 patient, and botulinum toxin injection in 1 patient.

Sixty-two granulomas in 50 patients were treated with the combination of inhaled triamcinolone and PPIs. Forty-seven patients with 58 vocal process granulomas completed treatment for a mean of 43.8 weeks (range, 3 to 84.6 weeks). Of those 47 patients, 16 also underwent voice therapy. In the cohort with complete treatment, 5 granulomas (9%) did not respond after a mean treatment course of 50 weeks (range, 30.3 to 78.3 weeks). Thirteen granulomas (22%) partially responded after a mean therapy course of 11 weeks (range, 3 to 30 weeks), and 40 (69%) completely responded after a mean therapy course of 21 weeks (range, 5.9 to 84.6 weeks). Temporally, complete or partial recovery was seen at 2, 4, and 6 months in 29%, 66%, and 79%, respectively (Fig 3). Three patients underwent surgical excision: 1 for biopsy and 2 others in whom conservative therapy failed (after 17 and 42 weeks). There were 3 recurrences: 2 in nonresponders after surgery and 1 in a complete responder. One patient developed oral thrush.

**DISCUSSION**

The epidemiology, presentation, and causes of vocal process granuloma in this study substantiate previous published results. A greater number of men were affected by vocal process granuloma (by a 4:1 ratio). This is likely due to the greater prevalence of vocal abuse in men, a result seen in this study.
Interestingly, the granulomas of all 11 women in this cohort followed recent intubation, an association that supports previous reports that women are more likely to sustain vocal process granuloma from intubation-related or surgical trauma. \cite{18-20} McFerran et al. \cite{18} suggested that the thinner mucosa in smaller larynges makes women vulnerable to trauma-related granuloma. In all patients included in this study, hoarseness represented the most common presenting symptom, seen in 72% of patients. Voice abuse (28%), intubation trauma (35%), and laryngopharyngeal reflux (59%) represented the 3 principal factors in the development of contact granuloma. Intubation trauma was significantly associated with development of granuloma in women, whereas vocal abuse was significantly associated with granuloma formation in men. These findings are suggestive of potential causes in men and women; however, this study was not designed to analyze causality.

In patients with unilateral granuloma, there was a significantly greater number of left-sided lesions (32) than right-sided lesions (9; \( p < 0.001 \)). This was significantly different from expected outcomes. This result is supported by other studies that have demonstrated a left-sided preponderance of vocal fold granulomas. \cite{16,21,22} This phenomenon could be related to intubation technique and the tendency for right-handed placement of an endotracheal tube to cause the tube to come into contact with the left vocal process. However, only 19 of the 54 patients were intubated, of whom 8 developed simultaneous bilateral granulomas, 9 developed left-sided granulomas, and 2 had right-sided lesions. Therefore, the left-to-right ratio of intubation-related unilateral contact granulomas is not substantially different from the overall ratio and likely does not explain the preponderance of left-sided lesions.

The presumptive pathophysiologic process of vocal process granuloma begins with trauma to the mucosa overlying the vocal process secondary to voice abuse, intubation injury, other trauma, and/or overexposure to acid reflux. \cite{8} This creates the ulceration commonly seen on histologic specimens along with subepithelial capillary proliferation and a mixed inflammatory infiltrate. \cite{18} Continued chemical exposure combined with mechanical trauma likely prop-
agates constant inflammation and exposure of the cartilaginous process, resulting in underlying peri-
chondritis, epithelial hyperplasia, and proliferation of granulation tissue. Fibrosis may also be 
seen on histologic analysis. The failure of surgical excision may be explained by its failure to address the principal causes of vocal process granuloma. Recurrence rates following surgical excision range from 25% to 92%. A large subset of patients in this study entered this study secondary to recurrent granuloma following surgery. Once placed on inhaled triamcinolone and a PPI, 2 (12%) partially responded and 13 (76%) completely responded—rates similar to the overall results. Only 3 patients in this study underwent surgical excision following initiation of medical therapy: 1 for biopsy and 2 others in whom conservative therapy failed. The small number of patients who required surgery further demonstrates the efficacy of combination medical therapy for treatment of vocal process granuloma.

Although antireflux and voice therapy have demonstrated some success in treatment of contact granuloma, the disease often recurs. In a retrospective review of 120 patients with contact granuloma, Yiitalo and Lindestad concluded that voice therapy did not significantly shorten healing time compared to an untreated cohort. Havas et al demonstrated excellent results for granulomas treated with antireflux medications, lifestyle modifications, and voice therapy, but still had 4 of 39 conservatively treated patients ultimately require gastric fundoplication to manage their gastroesophageal reflux and resolve their granuloma. Even in highly motivated patients, maintaining good vocal hygiene may decrease mechanical impact and laryngopharyngeal reflux; however, it may not be enough to completely resolve the vocal process inflammation. Reduction of healing time and treatment of refractory granulomas represent the principal basis for an additional medical mechanism to facilitate decreased local inflammation.

Inhaled steroids have a successful record in reducing local inflammation. Budesonide, beclomethasone, and triamcinolone have been used to treat nasal polyposis, allergic rhinitis, asthma, and chronic obstructive pulmonary disease. In 1999, Roh et al applied the inhaled topical steroid budesonide to the treatment of vocal process granuloma. The authors demonstrated resolution of 19 of 20 intubation granulomas within 12 months. The only side effect seen with inhaled budesonide in this cohort was a 10% rate of oral moniliasis. Although these outcomes were highly favorable, Roh et al solely included intubation granulomas, which have very high rates of resolution with medical therapy.

Our investigation applied the inhaled topical steroid triamcinolone to PPI therapy for combined medical treatment of vocal process granulomas resulting from various causes. Triamcinolone was used because it has a greater ratio of local anti-inflammatory effect to systemic absorption than does budesonide and it has an excellent long-term safety profile up to 12 months. Our therapy regimen evolved during the course of this study, thereby causing variations in PPI regimens and the use of voice therapy. The current treatment regimen is a PPI twice daily with inhaled triamcinolone 3 times daily for 6 to 8 weeks, augmented with voice therapy when appropriate. On follow-up, if there is partial or no resolution, we recommend continuation of therapy for another 6 to 8 weeks. After resolution of the granuloma, we discontinue the inhaled triamcinolone and taper the PPI over the next 2 to 3 months, after which patients follow up on an as-needed basis. We recommend this treatment regimen because it addresses multiple factors involved in the pathogenesis of vocal process granulomas, with the PPI diminishing the chemical insult from acid reflux and the topical triamcinolone reducing the local inflammatory response from mechanical and chemical trauma.

In a subset of 23 patients with vocal process granulomas or ulcers, Emami et al demonstrated an 87% rate of recovery following treatment with PPIs alone. No time to resolution was mentioned in their report. Wani and Woodson reported that all 18 patients treated with PPIs for vocal process granulomas responded to treatment; however, 2 of 4 partial responders required surgical excision, resulting in an 88% rate of recovery. The average time to complete resolution was 10.4 months. Our results demonstrated a 91% overall response rate with a median resolution time of 4.3 months. Seventy-nine percent of patients responded by 6 months, with complete recovery achieved in almost half of this cohort by 4 months and in two thirds by 1 year. Further demonstrating the success of this regimen, only 2 patients required surgical excision after failed combined medical therapy, a comparatively low rate of 3%. The 1 patient in whom oral candidiasis developed during use of inhaled triamcinolone was successfully treated with a 2-week course of topical nystatin while the triamcinolone regimen was continued. The rate of 1.9% in this cohort is consistent with the incidence of candidiasis in the use of inhaled triamcinolone in the asthma patient population (2.4%). Although oral candidiasis was an infrequent side effect in this study, care may be indicated in treating immunosuppressed individuals with inhaled triam-
cinolone.

The retrospective nature of this study, its small number of patients, and the lack of a case control limit its conclusions. The retrospective method resulted in a varied treatment protocol with a nonuniform PPI dosage schedule and duration and nonuniform follow-up times. Furthermore, less than one third of patients in this study received voice therapy for their granuloma, including only 8 of 15 patients identified as vocal abusers. A greater number of patients receiving voice therapy would optimize conservative multimethod treatment for vocal process granulomas. Finally, in 27 patients who presented with PPI therapy already initiated, the inhaled steroid was added to the regimen. Complete and partial responses in this group suggest that a beneficial response may be achieved with the steroid alone; however, this study did not assess inhaled steroid alone versus inhaled steroid with PPI. Future studies are necessary to study inhaled topical steroids’ effect on vocal process granulomas controlled for PPI use. Although difficult to organize and complete, a prospective multi-institutional study would potentially include a greater number of patients that could yield significant results on the benefits of combined medical therapy for the treatment of vocal process granulomas.

In this study, vocal process granulomas occurred more frequently in men, whereas women developed granulomas only after intubation. The significantly greater presence of left-sided granulomas supports other investigators’ findings, but lacks a clear cause, and is worthy of further investigation. The outcomes presented in this study support the therapeutic efficacy of inhaled triamcinolone combined with antireflux PPIs for treatment of vocal process granulomas with few side effects, a low recurrence rate, and no need for surgical excision. Inhaled topical steroids provide a direct anti-inflammatory mechanism to the laryngeal mucosa and represent a complementary therapy to PPI and voice therapy to improve treatment of vocal process granuloma.

REFERENCES
