Original Article



# Laryngeal contact granuloma after radiotherapy in patients with nasopharyngeal carcinoma: a case series

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**Background:** Laryngeal contact granuloma (LCG) is a benign hypertrophic lesion and phonatory injury after abnormal vocal behavior is regarded as its major etiology. Patients receiving radiation for non-laryngeal head and neck tumors are troubled by persistent voice impairment. The occurrence of LCG after radiotherapy for nasopharyngeal carcinoma (NPC) in our practice has implored us to re-exam their underlying etiology. We hypothesize that a proportion of LCG results from voice change caused by non-laryngeal head and neck cancer radiotherapy and firstly describe a distinct LCG population originated after radiotherapy for NPC with respect to the clinical profile, presentation, prognosis and response to treatment of patients.

**Methods:** We retrospectively reviewed the laryngoscopic examination and tumor study findings to elucidate the common clinical features of patients who presented with LCG after radiotherapy for NPC. All patients were regularly monitored with telescopic examination until lesions disappeared. Data on age, sex, clinical presentation, telescopic findings, management, latency time of lesion formation, remission time and clinical outcome were reviewed.

**Results:** The medical review identified 27 cases of LCG secondary to radiotherapy for NPC. All lesions had been diagnosed during routine endoscopy following radiation. The interval between radiation onset and endoscopic diagnosis was 3.77 months (range, 0.67–11 months). 20 cases were resolved through simple observation, 4 cases were resolved with the administration of proton pump inhibitors (PPIs), and 3 cases with a poor response to PPI therapy required subsequent surgical resection. The mean remission time in the observation and PPI groups was 4.42 months (range, 0.73–18.9 months) and 5.78 months (range, 2.17–14.63 months), respectively. All patients recovered completely and none experienced recurrence during a mean follow-up of 32.44 months (range, 5.6–71.67 months).

**Conclusions:** Iatrogenic granulomas of vocal process are presenting after radiation for non-laryngeal head and neck cancers. In contrast with spontaneous granulomas, these granulomas can be cured at high remission rates and low recurrence trend without specific intervention. Thus, simple observation may be sufficient for radiation-induced LCG.

**Keywords:** Laryngeal contact granuloma (LCG); radiotherapy (RT); nasopharyngeal carcinoma (NPC); non-laryngeal head and neck cancer

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## Introduction

Laryngeal contact granuloma (LCG) is a relatively uncommon, difficult-to-treat laryngeal disorder that accounts for 0.9–2.7% in adults with voice problems (1). Although it lacks invasive potential, LCG has high propensity for persistence and recurrence, regardless of treatment modality. Previous research indicates that the recurrence rate of LCG ranges from 37% to 97% (2), and that patients are especially prone to relapse when surgical resection is hastily applied (3). The persistence and recurrence of LCG is attributed to its multifactorial etiology.

Laryngeal contact granuloma develops when initial trauma to the mucosa at the vocal process causes the epithelium to ulcerate and chronic irritation or inflammation occurring during the healing process leads to epithelial hyperplasia. Etiological factors of LCG typically include hyperfunctional vocal behavior, laryngopharyngeal reflux (LPR), and intubation trauma. Hyperfunctional laryngeal adduction, especially referring to vocal abuse, throat clearing, and chronic coughing, manifest as "hammer-and-anvil" action of the vocal process, which results in repetitive phonotrauma (4). Glottic insufficiency and subsequent vocal hyperfunction can also result in phonatory injury and LCG formation (5). In all these scenarios, LPR acts as a significant potentiating cofactor, and irritation of gastric refluxate is associated with chronic inflammation of the posterior glottis (6). Intubation and other forms of clinical manipulation (7,8), such as bronchoscopy and esophagogastroduodenoscopy, can lead to mucosa injury and iatrogenic granulomas. Evidence suggests that when contributing factors are taken controlled, regression of granuloma tissue can be accelerated (3). Therefore, treatments of LCG in clinical practice attempt to be etiology driven, such as voice therapy to alleviate voice hyperfunctional action and anti-reflux medications to overcome LPR and prevent the injury from gastroesophageal reflux (9). However the treatment is still unsatisfactory with response rate of conservative treatment ranging from 20–44.3% (2) and it is mainly due to the unknown etiology and complex pathogenesis.

Recent data reveals that patients receiving radiotherapy for non-laryngeal head and neck cancer suffer from more severe voice impairment when compared with glottic tumor (10). Patients complain of increased vocal effort, breathiness and roughness while videostroboscopy demonstrates enhanced supraglottic activity and greater poster glottic gap. It is highly suggested that patients undergoing the aforementioned radiation develop voice disorder and subsequent vocal hyperfunction behavior. As in 2009 Carroll *et al.* (5) firstly reported that glottic insufficiency and subsequent voice hyperfunction for various causes was an underestimated etiology of LCG. Then the occurrence of LCG after radiotherapy for nasopharyngeal carcinoma (NPC) in our practice has implored us to re-exam the underlying etiology of these cases. We hypothesize that radiation against non-laryngeal head and neck cancer, such as NPC, may also be another etiology of LCG.

Our primary goal was to exam the LCG population specifically originating after radiotherapy for NPC, the most common type of non-laryngeal head and neck cancer in southern China. We are reporting our experience in an effort to describe their clinical features and try to determine whether radiation for non laryngeal head and neck cancer should be included in the various etiologic factors of LCG. To our knowledge, this work is the first to elucidate the characteristics of radiation-related LCG and thus may serve as a new clinical reference for pathophysiological research of laryngeal granuloma. We present the following article in accordance with the STROBE reporting checklist available at https://atm.amegroups.com/article/view/10.21037/atm-22-5817/rc).

### Highlight box

**Key findings**

- Laryngeal contact granuloma can result from radiotherapy for non-laryngeal head and neck cancer and harbors its unique characteristics.

**What is known and what is new?**

- Severe and persistent voice disorder and subsequent hyperfunctional vocal behaviors are attributed to radiotherapy for non-laryngeal head and neck cancer.
- A proportion of LCG originate from voice impairment and hyperfunctional vocal behavior caused by radiotherapy for non-laryngeal head and neck cancer.

**What is the implication, and what should change now?**

- Radiation-related LCG can be cured at high remission rates and low recurrence trend without specific intervention. Thus, simple observation may be sufficient for radiation-induced LCG.

## Methods

After receiving approval from the institutional review board of Nanfang Hospital, Southern Medical University (No. NFEC-201607-K2-01), this study was conducted in Nanfang Hospital, a tertiary referral center in southern

China. All patients who participated in this study signed an informed consent form. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). We retrospectively reviewed the medical records and a total of 27 patients who had completed radiotherapy after being diagnosed with nasopharyngeal carcinoma (NPC) were enrolled. These patients had presented with a chief manifestation of LCG during 1 year after radiotherapy for NPC and were confirmed by telescopic examination, between January 2010 and September 2021. All patients were regularly monitored with flexible laryngoscope until lesions disappeared.

Patients' demographic data were retrospectively collected and are summarized in *Table 1*. Granuloma size was graded as I–IV based on the staging system proposed by Farwell *et al.* (11). In cases of simultaneous bilateral granuloma, the lesions were graded based on the size of the larger lesion. Remission was defined as the disappearance of the granuloma mass in the endoscopic view.

### *Statistical analysis*

All data were analyzed with SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and the analysis in our study were all descriptive. Two-sided P value <0.05 was interpreted as being statistically significant. Latency time was defined as the time between the onset of radiotherapy and the endoscopic diagnosis of LCG. Remission time was defined as the interval between the diagnosis of LCG and its disappearance in the endoscopic view. Student's t-test was applied to determine the differences in latency and remission time according to different clinical parameters.

## Results

### *Patient demographic characteristics*

Medical records of 27 patients who were diagnosed with LCG after radiotherapy for NPC were collected, and their demographic data are summarized in *Table 1*. These patients included 23 males and 4 females, who had a mean age of 47.85±8.26 years (range, 34–67 years). In all cases, the tumor histopathology was undifferentiated squamous cell carcinoma. Two patients had no initial staging or therapy data recorded due to receiving treatment elsewhere. According to the 2008 American Joint Committee on Cancer staging system, of the 25 patients for which staging information was available, 1 case was stage I, 14 cases were stage III, and 10 cases were stage IV. All 25 of these patients received radiation therapy delivered in the form of intensity-modulated radiotherapy by 6-MV photons, and the irradiation dosage ranged from 68 to 71 Gy. Patients receiving radiotherapy in our hospital finished concurrent chemotherapy (CRRT group) during irradiation, and 18 patients underwent induction chemotherapy with cisplatin and paclitaxel (IC group), as well as concurrent chemotherapy.

### *Morphologic features of LCG*

After the commencement of radiotherapy, smooth, pedunculated, or sessile, and red or pale masses were identified on the vocal process of the arytenoid cartilage. All lesions were observed with regular monitoring through telescopic examinations. No patients complained of hoarseness or recalled voice changes. Pain or dysphagia was noted in 20 cases. Twenty-one patients presented with unilateral LCG (12 left sided and 8 right sided) (*Figure 1*), while 7 patients presented with simultaneous bilateral masses (*Figure 2*). Lesions were graded according to Farwell *et al.*'s LCG staging system (11). There were 14 cases with stage I, 11 cases with stage II, and 2 cases with stage III lesions (*Figure 3*). Baseline laryngeal reflux signs before treatment were evaluated using the reflux finding score (RFS). Of the 19 cases available for reflux evaluation, 12 cases presented with LPR-likely signs (RFS ≥7) and 7 cases had LPR-unlikely signs (RFS <7).

### *Management and outcome of LCG*

Of the 27 patients in the study, 7 were initially treated with a daily oral dose of proton pump inhibitors (PPIs). Among these cases, 3 patients required surgical excision due to showing a poor response to PPI therapy. For the 4 patients who responded favorably to PPI therapy, complete remission was observed within 2.17–14.63 months (mean 5.78±5.89 months). The remaining 20 cases received only observation and no specific medication or voice therapy. Their lesions resolved completely within 0.73–18.9 months, with a mean time of 4.42±4.25 months. In the observation group, 42.11% cases achieved rapid remission within 3 months, and 78.9% cases within 6 months. With the exception of 1 patient who was lost to follow-up, none of these cases experienced lesion recurrence during a mean follow-up of 32.44±20.54 months (range, 5.6–71.67 months). All patients in our study showed no evidence of tumor

 

**Table 1** The demographics and outcome measures of the 27 patients

| Case | Age (years) | Gender | NPC treatment | LCG stage | Latency time (months) | LCG treatment | Remission time (months) | Recurrence |
|---|---|---|---|---|---|---|---|---|
| 1 | 47 | M | NA | II | 2.07 | PPI | 2.17 | – |
| 2 | 51 | M | IC + RT + CCRT | III | 11.00 | PPI + surgery | – | – |
| 3 | 52 | M | RT + CCRT | II | 4.13 | PPI + surgery | – | – |
| 4 | 52 | M | IC + RT + CCRT | II | 7.33 | Observed | 11.07 | – |
| 5 | 57 | F | IC + RT + CCRT | II | 5.40 | Observed | 2.90 | – |
| 6 | 58 | M | IC + RT + CCRT | I | 4.50 | Observed | 4.97 | – |
| 7 | 40 | M | RT + CCRT | III | 1.17 | Observed | 1.77 | – |
| 8 | 46 | M | IC + RT + CCRT | I | 4.70 | Observed | 8.47 | – |
| 9 | 36 | M | IC + RT + CCRT | I | 3.20 | Observed | 3.73 | – |
| 10 | 54 | M | RT + CCRT | I | 0.77 | Observed | 0.73 | – |
| 11 | 39 | M | IC + RT + CCRT | II | 4.20 | PPI | 2.70 | – |
| 12 | 54 | M | IC + RT + CCRT | II | 0.67 | Observed | 3.47 | – |
| 13 | 43 | F | RT + CCRT | I | 0.73 | Observed | 0.93 | – |
| 14 | 34 | M | RT + CCRT | I | 4.53 | PPI | 3.60 | – |
| 15 | 39 | F | IC + RT + CCRT | II | 4.60 | PPI + surgery | - | – |
| 16 | 53 | M | IC + RT + CCRT | I | 4.63 | Observed | 2.77 | – |
| 17 | 42 | F | IC + RT + CCRT | II | 2.17 | Observed | 5.87 | – |
| 18 | 50 | M | IC + RT + CCRT | I | 4.97 | Observed | 0.93 | – |
| 19 | 43 | M | IC + RT + CCRT | II | 1.57 | PPI | 14.63 | – |
| 20 | 47 | M | RT + CCRT | I | 1.83 | Observed | 18.90 | – |
| 21 | 51 | M | IC + RT + CCRT | I | 1.17 | Observed | 3.30 | – |
| 22 | 58 | M | IC + RT + CCRT | I | 2.60 | Observed | 4.43 | – |
| 23 | 34 | M | IC + RT + CCRT | I | 2.07 | Observed | 1.17 | – |
| 24 | 49 | M | NA | I | 1.27 | Observed | 1.27 | – |
| 25 | 40 | M | RT + CCRT | II | 10.60 | Observed | 3.13 | – |
| 26 | 67 | M | IC + RT + CCRT | II | 7.43 | Observed | 6.60 | – |
| 27 | 56 | M | IC + RT + CCRT | I | 2.47 | Observed | 8.63 | – |
| Mean | 47.85 | | | | 3.77 | | 4.92 | |

NPC, nasopharyngeal carcinoma; LCG, laryngeal contact granuloma; M, male; F, female; NA, unavailable; RT, radiotherapy; IC, induction chemotherapy; CCRT, concurrent chemotherapy; PPI, proton pump inhibitor.

recurrence or metastasis after radiotherapy, and no patient had a second primary cancer during the long-term follow-up.

### *Latency time of LCG*

In our study, all lesions were identified after the onset of NPC radiotherapy. The latency time ranged from 0.67–11 months, with the mean time being 3.77±2.78 months. Of the masses, 51.85% formed within 3 months following the start of irradiation and 85.19% formed within 6 months. Latency time did not display significant differences according to basic characteristics, including sex (P=0.68), age (P=0.69),

 

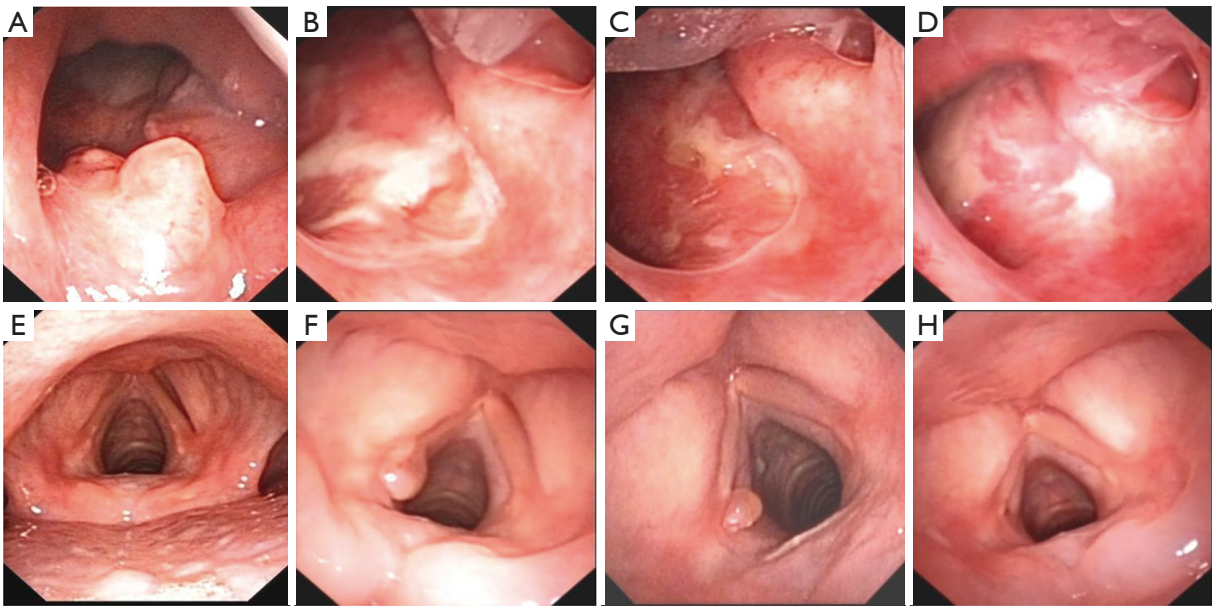


**Figure 1** Left vocal fold lesion after RT for NPC (T4N2M0). (A) A 43 year old man was diagnosed with NPC (T4N2M0) and (E) meanwhile no evidence of LCG was identified. (F) Approximately one month after radiotherapy started (B) the tumor vanished while the left vocal process was observed with a grade III granuloma. (G) A year later the lesion only slightly regressed. (H) During a 2 year follow up the lesion disappeared and showed no recurrence. (C,D) This patient had no sign of tumor recurrence around the nasopharynx or skull base. RT, radiotherapy; NPC, nasopharyngeal carcinoma.

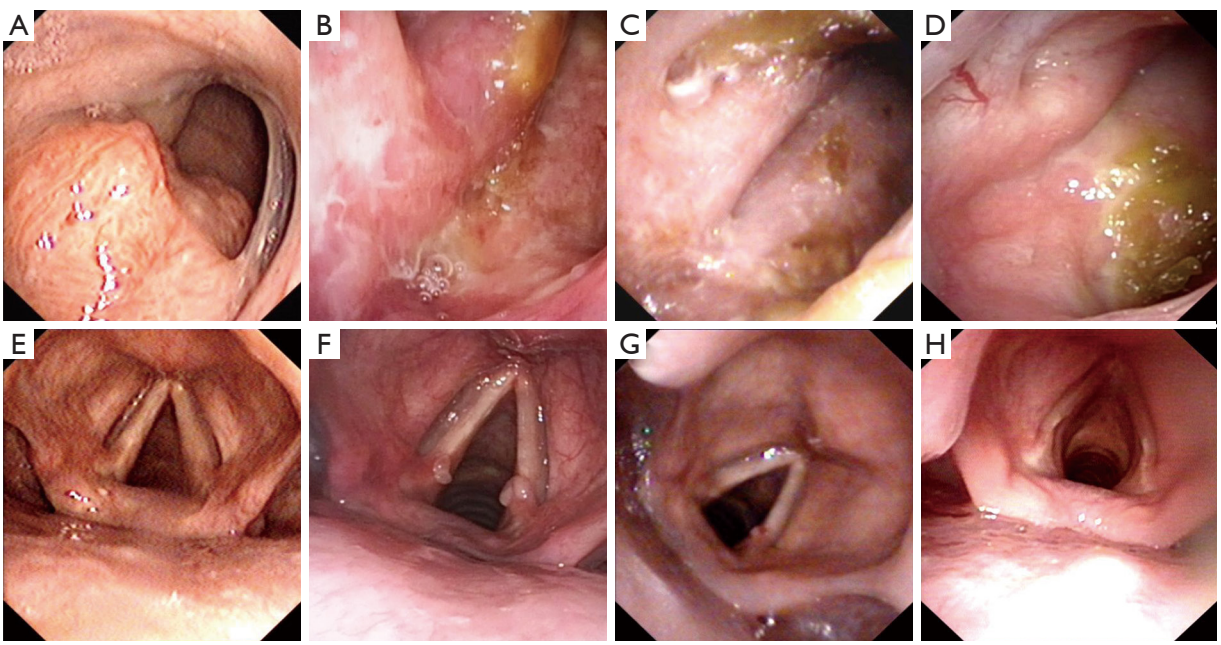


**Figure 2** Bilateral lesions after RT for NPC (T3N2M0). (A) A 39- year- old man was diagnosed with NPC (T3N2MO) and (E) LCG was not found initially. Four months later, (B) nasopharyngeal tumor vanished postradiotherapy and (F) LCGs were present with gradeIIulcerative lesions bilaterally. (G) After three months the left lesion achieved completely remission and the right side largely regressed. (H) No relapse of LCG was recorded In the 6-month followup. (C)(D) This patient had no evidence of tumor recurrence around the nasopharynx or skull base. RT, radiotherapy; NPC, nasopharyngeal carcinoma.

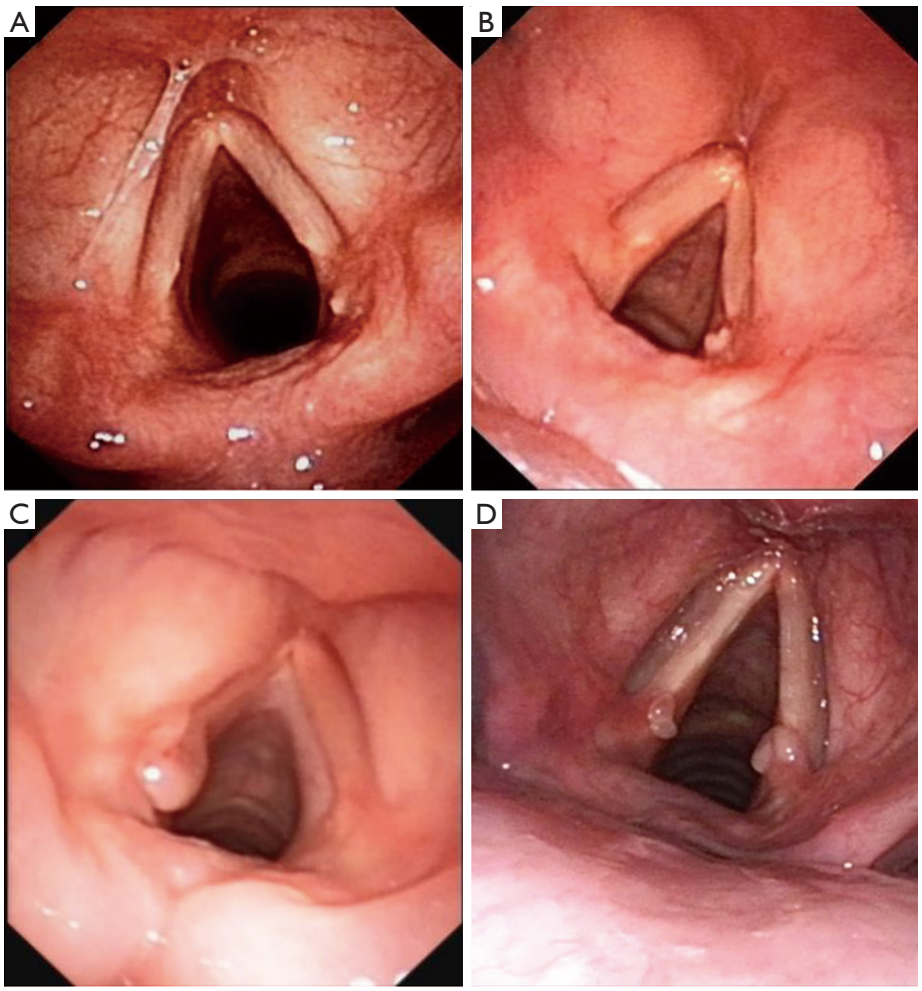


**Figure 3** Morphologic characteristics of LCG with different size. (A) Unilateral keratotiic lesion of grade I. (B) Unilateral ulcerative lesion of grade II. (C) Unilateral exophytic lesion of grade III. (D) Bilateral bilobular lesions. LCG, laryngeal contact granuloma.

unilateral/bilateral lesion (P=0.632), lesion size (P=0.228), and chemotherapy (P=0.559). Concerning the potential effect of LPR on LCG formation, comparison showed that the mean latency period in the LPR-likely group (mean 2.84±1.68 months) was shorter than that in the LPR-unlikely group (mean 4.66±3.00 months). Despite the lack of significant difference between the groups (P=0.107), patients with high LPR likelihood were more prone to LCG development during irradiation than were those with low LPR likelihood (*Table 2*).

### *Remission time of LCG*

With the exclusion of the 3 cases that required surgical intervention, the remission time of the patients (n=24) was evaluated. Remission time was not associated with sex (P=0.504), age (P=0.542), unilateral/bilateral lesion (P=0.796), lesion size (P=0.492), chemotherapy (P=0.825), or LCG treatment (P=0.691). The impact of LPR on LCG remission was also assessed (n=16). No significant difference was found (P=0.261) but an interesting trend was observed that the remission time in the LPR-likely group (mean 4.70±3.78 months) was longer than that in the LPR-unlikely group (mean 2.41±1.02 months). This finding indicated that LCG was resolved more easily and promptly in the LPR-unlikely group than the LPR-likely group (*Table 3*).

## Discussion

The LCGs in this study were presumed to be radiation-

**Table 2** Factors influencing the latency time of laryngeal contact granulomas

| Characteristics | Occurrence No. | Latency time (months) (mean ± SD) | P value |
|---|---|---|---|
| Sex | | | 0.68 |
| Male | 23 | 3.86±2.90 | |
| Female | 4 | 3.23±2.16 | |
| Age (years) | | | 0.69 |
| ≥45 | 17 | 3.94±2.80 | |
| <45 | 10 | 3.48±2.87 | |
| Reflux evaluation | | | 0.107 |
| LPR-likely (RFS ≥7) | 12 | 2.84±1.68 | |
| LPR-unlikely (RFS <7) | 7 | 4.66±3.00 | |
| Unilateral/bilateral lesion | | | 0.632 |
| Unilateral | 20 | 3.93±3.15 | |
| Bilateral | 7 | 3.32±1.32 | |
| LCG grading | | | 0.228 |
| Small (III) | 25 | 3.58±2.42 | |
| Large (III IV) | 2 | 6.09±6.95 | |
| Chemotherapy | | | 0.559 |
| CRRT group | 7 | 3.39±3.54 | |
| (IC + CCRT) group | 18 | 4.15±2.58 | |

LPR, laryngopharyngeal reflux; RFS, reflux finding score; LCG, laryngeal contact granuloma; CCRT, concurrent chemotherapy; IC, induction chemotherapy.

**Table 3** Factors influencing the remission time of the laryngeal contact granulomas

| Characteristics | Occurrence No. | Remission time (months) (mean ± SD) | P value |
|---|---|---|---|
| Sex | | | 0.504 |
| male | 21 | 5.16±4.77 | |
| Female | 3 | 3.23±2.49 | |
| Age (years) | | | 0.542 |
| ≥45 | 15 | 5.37±4.84 | |
| <45 | 9 | 4.17±4.20 | |
| Reflux evaluation | | | 0.261 |
| LPR-likely (RFS ≥7) | 12 | 4.70±3.78 | |
| LPR-unlikely (RFS <7) | 4 | 2.41±1.02 | |
| Unilateral/bilateral lesion | | | 0.796 |
| Unilateral | 18 | 4.78±4.59 | |
| Bilateral | 6 | 5.35±4.85 | |
| LCG grading | | | 0.492 |
| Small (III) | 23 | 5.06±4.60 | |
| Large (III IV) | 1 | 1.77 | |
| Chemotherapy | | | 0.825 |
| CRRT group | 6 | 4.84±6.98 | |
| IC + CCRT group | 16 | 5.35±3.73 | |
| LCG treatment | | | 0.691 |
| Observation | 20 | 4.75±4.40 | |
| PPI | 4 | 5.78±5.93 | |

LPR, laryngopharyngeal reflux; RFS, reflux finding score; LCG, laryngeal contact granuloma; CCRT, concurrent chemotherapy; IC, induction chemotherapy; PPI, proton pump inhibitor.

induced because all the lesions originated secondary to NPC radiotherapy. They harbored unique clinical features, namely high potential for spontaneous resolution and low recurrence. However, how radiation for non-laryngeal head and neck cancer contributes to laryngeal granuloma formation has not been reported before.

In patients undergoing radiotherapy for head and neck cancer, the larynx receives incidental radiation even in the absence of laryngeal disease. Preliminary investigation has provided evidence that with both wide-field radiotherapy (10) and intensity-modulated radiotherapy (12), patients with non-laryngeal head and neck cancer suffer from voice impairment to a greater extent than those with glottic tumors. Voice changes are prominent at 3 months (13) post treatment and can take up to 8 years (14) to completely normalize after treatment. Such changes are associated with radioactive effects on the vocal fold, such as mucosa edema (15), fibrosis (16-18), and dryness (19), in addition to muscle atrophy. Besides, changes to the vocal tract, referring to the airway above the glottis, also play an indispensable role in vocal fold vibratory behavior (20). Eventually, hyperfunctional vocal action compensates for these abnormal phonation activities, as observed stroboscopically, with supraglottic constriction and ventricular activity (10). Vocal hyperfunction manifests as a repetitive "hammer and anvil"

action and thus, inevitably causes mucosal trauma of the vocal process. LCGs presumably develop as a result of the compensatory vocal action secondary to radiation-induced voice alteration. Recently, Sreenivas *et al.* (21) successfully used voice rehabilitation to alleviate inefficient compensatory vocal behavior and improve vocal performance in patients with non-laryngeal head and neck tumors after radiation.

Eliminating causative risk factors constitutes the first step in LCG management (2). Generally, laryngeal granulomas are divided by etiology into spontaneous granulomas and iatrogenic granulomas (22). Radiation-related LCGs, like intubation granulomas, are ascribed to a solitary, temporary event of laryngeal injury, whereas spontaneous granulomas usually originate from a chronic pattern of repetitive phonotrauma. Therefore, once etiological factors are taken under control, iatrogenic granulomas usually resolve quickly. Radiation-related LCGs in our series resolved within 17.7 weeks (approximately 4 months), while in the study of Wang *et al.* intubation LCG within 23.9 weeks (approximately 6 months), and spontaneous LCG within 33.4 weeks (approximately 8 months) (23). Further, both intubation and radiation-related LCGs exhibit a propensity for self-remission, whereas spontaneous LCGs rarely disappear without intervention (4). More importantly, iatrogenic LCGs do not appear to exhibit a high tendency toward recidivism as compared to other posterior glottic lesions (8,22), and no cases of recurrence were recorded in our study. On this basis, we propose that radiation-related LCG should be deemed a disparate entity, or another type of iatrogenic granuloma, and minimal management may be pursued if no obvious symptoms are reported.

Inhibition of gastric refluxate in the larynx cavity is recommended as a first-line treatment for LCG management (9). LPR has been demonstrated to be not only a potential factor for LCG development, but also an independent risk factor for severe radiation-induced mucositis in the prelaryngeal area. Previously, Eguchi *et al.* (24) reported that patients with a high RFS, indicating high LPR likelihood before radiation, were more susceptible to radiation damage and developed severe laryngeal mucositis earlier than patients with low LPR likelihood. When PPI therapy was administrated, the mucositis was quickly ameliorated (25). Therefore, we believe that under chronic stress of LPR, the laryngeal mucosa may be vulnerable to irradiation damage and may well facilitate radiation-related LCG formation after radiation. Following Eguchi *et al.*'s study (24), we used the RFS for LPR assessment before radiotherapy in our series. Unexpectedly, LCG tended to develop sooner post radiation in the high LPR likelihood group than in the low LPR likelihood group but had a longer remission time. Even though no statistical significance was observed between the groups, this result reinforces the contribution of LPR to the special entity of LCG. The recession time of PPI group was not significantly shorter than observation group as previously reported (2). This observation may largely be due to the small sample size in our study and a prospective study may be warranted in the future.

Our study had some limitations that need to be addressed. First, this was a retrospective study and the sample size was small. Further, the RFS alone is not sufficient as a measure of LPR involvement in LCG. The gold standard of LPR objective testing is pH monitoring, and the salivary pepsin test is another promising test. However, as a retrospective study, we were unable to conduct a reflux symptom index questionnaire, pH monitoring, or saliva collection. Nevertheless, despite of the aforementioned limitations, our study, for the first time, presents the characteristics of LCG secondary to radiation of non-laryngeal cancer and serves as a valuable clinical reference for LCG research.

## Conclusions

The present study describes 27 cases of LCG after radiotherapy for nasopharyngeal carcinoma. In most of these cases, spontaneous remission was achieved without intervention and no relapse occurred. Granulation tissue in patients with a high RFS before radiation tends to develop quicker but have a longer remission time than in those with a low RFS.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5817/rc

*Data Sharing Statement:* Available at https://atm.amegroups.

com/article/view/10.21037/atm-22-5817/dss

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5817/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All patients who participated in this study signed an informed consent form, and this study was approved by the Institutional Review Board of Nanfang Hospital, Southern Medical University (No. NFEC-201607-K2-01). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).



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