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A Giant Granuloma of the Vocal Process after Double-Lumen Bronchial Catheter Insertion: A Rare Case Report and Literature Review

Xiaoqin Zeng[1], Xiaoyu Xi[1], Shun Guo[1], Ya Zhao[1], Bo Li[2], Rui Xia[1*]

[1]Department of Anesthesiology, The First Affiliated Hospital of Yangtze University, Jingzhou, China
[2]Department of Anesthesiology, The First Affiliated Hospital of Hubei University of Science and Technology, Tianmen, China

Email: zengxiaoqin320@sina.com, 1914674342@qq.com, 510318506@qq.com, 941267585@qq.com, 987085193@qq.com, *879560350@qq.com

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Abstract

Background: Double-lumen endotracheal (DLT) is commonly used for one-lung ventilation and lung separation during thoracic surgery. There are case reports of medically induced laryngeal granulomas, mainly in patients after single-lumen endotracheal (SLT) tube intubation and tracheotomy, and giant granulomas of the vocal cords due to double-lumen bronchial tube insertion have rarely been reported. Case presentation: A 49-year-old female patient underwent single-port thoracoscopy after DLT intubation as well as a wedge resection of the lower lobe of the left lung, which caused giant vocal process granulomas (VPGs) postoperatively. Based on a retrospective analysis of the general condition, current medical history, past medical history, and visual laryngoscopic observation of the vocal folds tissue, which ruled out preoperative vocal fold granuloma formation, we hypothesized that double-lumen bronchial catheter intubation may have been the primary cause of her vocal fold granuloma formation. Conclusions: Giant granuloma of the vocal folds after DLT insertion is a rare postoperative complication; therefore, if DLT intubation is to be performed, the anesthesiologist should choose an appropriate intubation plan and deal with it promptly to avoid the risk factors to ensure that the patient's perioperative period is safe and smooth. In addition, if postoperative complications are encountered, they should be followed up and observed on time.

Keywords

Vocal Process Granulomas, Double-Lumen Endotracheal, Single-Lumen Endotracheal, Case Report

1. Introduction

Due to the prevalence of COVID-19, chest computed tomography (CT) has become a routine screening method for most outpatients, resulting in an increasing number of pulmonary nodules being detected. Thoracoscopic pulmonary nodule resection is the most appropriate and effective method for the diagnosis and treatment of pulmonary nodules, providing the necessary histopathologic information for definitive diagnosis, staging, and initial treatment [1]. Successful surgical treatment is inextricably linked to anesthesia. Most thoracoscopic procedures are performed under general anesthesia with the insertion of a double-lumen endotracheal (DLT), which allows one-lung ventilation and lung separation during thoracic surgery. In 1932, Clawsen had described laryngeal granulomas for the first time as a result of endotracheal intubation, prompting other authors to investigate their predisposing factors [2] [3]. Risk factors associated with the development of postintubation laryngeal granuloma have been shown in numerous case reports and clinical findings to include female gender, traumatic intubation, prolonged intubation, inappropriate catheter size, high trocar pressure, and the presence of a nasogastric tube. However, there is no consistent single risk factor for the development of chronic laryngeal granuloma [4]. Usually, the majority of case reports of vocal granulomas are in patients with single-lumen endotracheal (SLT) intubation and tracheotomy. However, there are fewer case reports of vocal granuloma formation after DLT intubation. In this paper, we report a case of giant granuloma of the vocal folds occurring after DLT, resulting in airway obstruction, dyspnea, and a difficult airway that required a second intubation for surgical treatment.

2. Case Presentation

The patient, a 49-year-old woman, height 158 cm, weight 51 kg, farmer, was admitted to the hospital with "hoarseness of voice and respiratory effort for one month, aggravated for one week". The patient's general condition was acceptable, with no history of gastroesophageal reflux, no family history of granuloma formation in the vocal folds, no denial of hypertension, diabetes mellitus, cardiovascular disease, etc., and the nature of her work had nothing to do with her speech, and she had no bad hobbies (smoking, alcoholism, drug addiction, etc.). Usually in good health and not taking any medication. Physical examination: T 36.5˚C, P 76 times/min, R 20 times/min, BP 121/74 mmHg (1 mmHg = 0.133 kPa); clear consciousness, cooperation in physical examination, mouth opening > 3 horizontal fingers, nail-chin distance > 4 horizontal fingers, Mallampati grade I; cardiac function grade I; both lungs have clear respiratory sounds, and no obvious dry and wet rales were heard; no pathological murmurs were heard in the heart valves. No pathologic murmurs were heard in the valves, the abdomen was soft, with no pressure or rebound pain, the liver and spleen were not detected in the subcostal region, and there was no edema in the lower limbs. Previously, she was hospitalized in the Department of Thoracic Surgery of our

hospital for surgical treatment of single-port thoracoscopic wedge resection of the left lower lobe of the lung due to a nodule in the left lower lobe of the lung three months ago. Before induction of anesthesia, 5 L/min of pure oxygen was given by mask inhalation, and 5 minutes later, a rapid sequence of anesthesia induction was performed using penehyclidine hydrochloride injection 0.25 mg, sufentanil 30 μg, propofol 100 mg, and rocuronium bromide injection 50 mg to induce general anesthesia, and the mask ventilation after the induction was smooth, with a good thoracic rise and fall. Three minutes later, a right barbless 35 Fr/C (11.7 mm) DLT (Covidien LLC, USA) was inserted under visual laryngoscopy, and with adequate paraffin oil lubrication in the first 1/3 before intubation. The first 1/3 of the double-lumen bronchial catheter was fully lubricated with paraffin oil before intubation, and the surface of the vocal folds was smooth under visual laryngoscopy, with no obvious redness and swelling of the vocal folds. When the bronchial sleeve at the front of the catheter passed the vocal folds, the catheter was rotated 90 degrees to the left (counterclockwise rotation), the DLT was gently pushed to a depth of 26 cm, and the intubation was smooth, and then the catheter was positioned with an electronic soft microscope in a good alignment, and the DLT was fixed in the middle of the mouth. Intraoperative anesthesia was maintained with inhalation of 1 vol% sevoflurane, intravenous infusion of dexmedetomidine 0.6 μg/kg/h, remifentanil 0.12 - 0.25 μg/kg/min, keeping BIS 40 - 55, and adjusting the rate of drug infusion at an appropriate time. Under ultrasound guidance, the left radial artery and right internal jugular vein were punctured and cannulated with continuous pressure measurement, and the vital signs were stable during the operation. The operation lasted 80 minutes, and the patient was extubated at the end of the operation after a good recovery of spontaneous respiration and awakening from anesthesia. The anesthesia lasted 144 minutes, and the patient was stable during the awakening period, with no choking, coughing, or agitation, and spontaneous respiration was recovered freely. After extubation, the patient was sent to the recovery room for further observation and was safely sent back to the ward after Steward's awakening assessment of 6 points. Symptomatic treatments such as anti-infection, nebulization, and hemostasis were given in the ward. On the first postoperative day after anesthesia, the patient was visited with chest tightness, no other discomfort such as hoarseness, and continued to be given symptomatic treatment. Postoperative pathology report: (left lower lung) pulmonary mycosis, probably Aspergillus. The patient was discharged from the hospital after no discomfort, and no abnormality was found in the follow-up examination. More than two months after the operation, the patient reported hoarseness with respiratory effort and occasional foreign body sensation, which was not taken seriously at that time and was not treated. On the 105th day after the operation, the patient reported that hissing and respiratory effort had worsened and was admitted to the outpatient clinic of our hospital. Laryngoscopy showed non-specific granuloma of the larynx (**Figure 1**), and she was admitted to the hospital with the diagnosis

of "laryngeal neoplasm: non-specific granuloma". CT of the head and neck showed that the larynx was occupied in the vocal folds, the nature of which was to be investigated (Figure 2). Other imaging and tests did not show any significant abnormal findings. Vocal cord lesion resection was proposed to be performed on September 22 under general anesthesia with awake tracheal intubation (ID 5.5 mm, spring tube). Histologic examination of the resected lesion showed a large amount of granulation tissue in the vocal cord mesenchyme (Figure 3). The patient was followed up on the first day after anesthesia without dyspnea, no pharyngeal foreign body sensation, and hissing improved significantly. On the third postoperative day the patient was discharged from the hospital without significant discomfort.

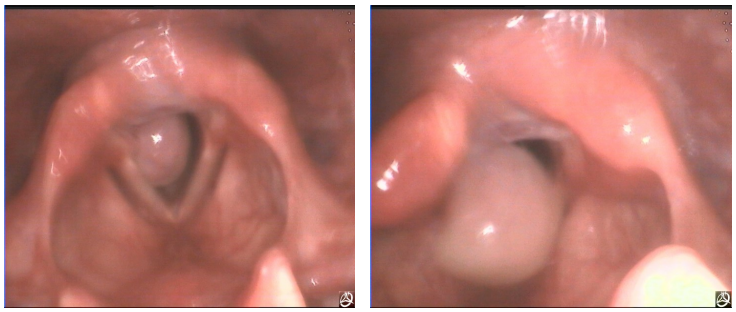

Figure 1. Changes on fiberoptic laryngoscopy 105 days after thoracic surgery. Fiberoptic laryngoscopy revealed granulation tissue in the arytenoid cartilage region of the right vocal cord.

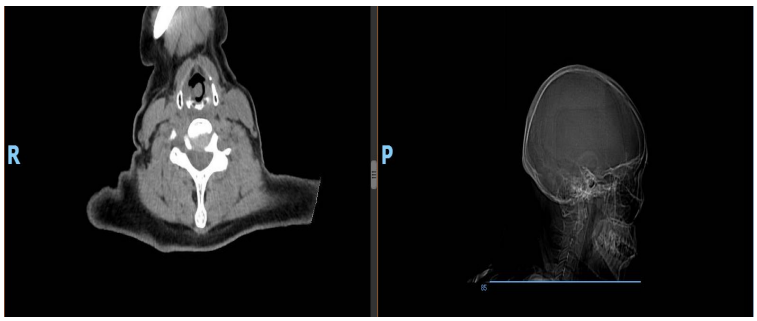

Figure 2. Computed tomography of the chest shows a localization in the vocal folds of the larynx. Computed tomography of chest cross-section.

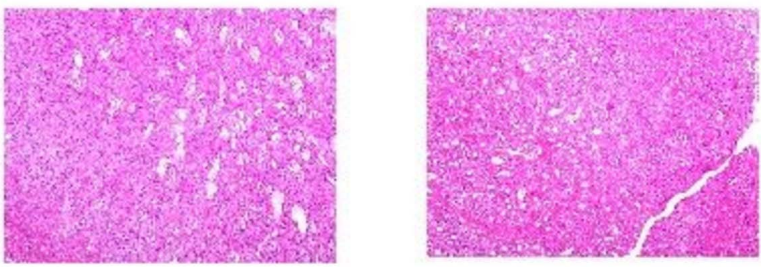

Figure 3. Pathologic slide image. Pathology report after excision of vocal cord polyp showing right vocal cord polyp with a large amount of granulation tissue in the interstitium (HE, original magnification ×100).

3. Discussion and Conclusions

Vocal process granulomas (VPGs) are usually benign lesions located in the posterior third of the vocal folds, mainly at the level of the arytenoid cartilage vocal fold elevation, and are translucent, white, or pink smooth-surfaced swellings, most often unilateral, but may be bilateral. They are usually associated with irritation of the laryngeal mucosa by mechanical injury from tracheal intubation or inappropriate vocalization, recurrent infections of the upper respiratory tract, exposure to irritant causative agents (e.g., dust, chemicals, and cigarette smoking), and gastroesophageal reflux [5] [6] [7], manifesting as mucosal damage resulting in the development of granulation tissue. Usually, the former is referred to as membranous traumatic vocal fold granulomas, intubation granulomas (IGs); the latter is referred to as contact granulomas (CGs), retrosternal granulomas; when these causes are ruled out, it is referred to as idiopathic granulomas. There is no pathological difference between IGs and CGs, which are not actual granulomatous processes in a pathological sense (as they lack the aggregation of mononuclear and polymorphonuclear histiocytes) [8] but rather are a recurrent repair process, in which intact or ulcerated squamous epithelium is covered by granulation tissue. Histological analysis shows marked proliferation of blood vessels in the lamina propria of the granulation tissue, the presence of severe inflammation as well as lymphocyte infiltration, while under the transmission electron microscope (TEM), studies reveal intracytoplasmic changes in other ultrastructures such as fibroblasts, where intracellular junctions become wider in response to changes in the structure of the bridging granules, indicating cellular dysfunction and damage [3]. Although vocal fold granulomas may recur locally (especially if the initial predisposing cause is still present), it has no potential for precancerous transformation.

Risk factors associated with vocal granuloma formation after tracheal intubation are positively correlated with time of intubation, trocar pressure, catheter type, and other factors.

In clinical practice, medically induced membranous vocal fold granulomas resulting from tracheal intubation or surgery with other upper airway instruments are a recognized but rare complication that takes about 21 days to appear and resolves spontaneously in about three months in most cases [9]. A study that included a sample of 393 patients showed that vocal fold granulomas caused after tracheal intubation accounted for approximately 14% of patients with acute laryngeal injury and dysfunction [10]. Among another sample of 234 patients (with double-lumen tubes), 42/234 patients (18%) developed complications, of which double-lumen tube placement caused airway injury in about 0.4% [11]. They are usually associated with prolonged intubation, which is further exacerbated, especially by intubation for more than 10 - 12 days, but may also occur after less than 24 hours of intubation. In a prospective study, Santos *et al.* [9] evaluated risk factors for laryngeal injury in 97 patients after tracheal intubation for more than 3 days (3 - 28 days, mean 9 days). They found that 97% of the

subjects suffered from some form of laryngeal injury ranging from mild mucosal erythema to ulceration, granuloma formation, or vocal fold immobilization. Laryngeal granulomas were present in 44% of these patients and most granulomas (57%) appeared an average of 4 weeks after extubation, with the associated risks being the presence of a nasogastric tube and the duration of intubation. It is worth noting, however, that granulomas caused by prolonged intubation do not necessarily imply damage to the laryngeal mucosa during pre-tracheal tube insertion; they can simply be caused by excessive pressure on a properly placed tracheal tube or by irritation from a foreign body. Some animal studies have shown that when the pressure of the sleeve on the tracheal wall reaches 40 - 80 mmHg, the tracheal mucosa that is beginning to ischemia necrosis and detachment, interruption of blood flow between the tracheal cartilage, and even cause perforation of the tracheal wall, rupture, and other serious complications; when the pressure of the airbag reaches 100 mmHg, maintained for 15 minutes, the basement membrane that is beginning to be separated, and the mucosal stroma is exposed to the 4 hours after the damage and inflammation can invade the cartilage [12]. This is because anatomically, the hard laryngeal cartilage is covered with less soft tissue, creating an area of poor tissue compliance that is unable to cushion mechanical trauma and is prone to local tissue microischemia under prolonged intubation and/or high balloon pressure conditions and is therefore susceptible to mucosal injury. Usually, postintubation laryngeal granuloma formation is a late complication associated with intubation injury, which is rare in pediatric patients, especially if the intubation time is short. This is attributed to certain characteristics of the pediatric larynx as well as some conventional consensus, such as the looser mucous membranes over and under the pediatric glottis and the relatively greater ability of children to heal from trauma. Children rarely require prolonged intubation compared with adults, and there is a high consensus among anesthesiologists for the use of smaller tracheal tubes and conservative tracheal sleeve pressures for pediatric patients. Vocal granulomas are predominantly seen in males, except postintubation granulomas. In contrast, the majority of intubation-related laryngeal granulomas were in female patients, which may be related to their lower vocal fold ratio [13]. The vocal fold ratio is the mathematical ratio between the midsagittal dimension of the intermembranous region of the larynx and the midsagittal dimension of the intercartilaginous region during inspiration. This relatively low ratio (1.2 in males and 1.0 in females) protects the arytenoid cartilage region of the female larynx from physical injury when vocalizing with force and reduces bilateral arytenoid cartilage collisions. However, it also puts women at a greater relative risk of injury to the laryngeal mucosa due to the smaller laryngeal framework and lumen, making them more susceptible to post-tracheal intubation granuloma. Other researchers have found that for the same tracheal pressure and intubation time, the larger the catheter model, the greater the damage to the tracheal wall. This is because the back part of the larynx is often in close contact with the V-shaped

glottis. If a tracheal catheter of a larger caliber is used, this area becomes compressed and causes tissue ischemia, in which case one quickly observes ulceration of the laryngeal surface and necrosis of the mucous membrane after extubation. However, most post-extubation laryngeal injuries will be more susceptible to mechanical damage and tracheal sleeve pressure when the patient has a specific condition such as inadequate tissue perfusion, such as occurs in patients with frailty, diabetes mellitus, hypertension, coronary artery disease, or systemic infection [14].

DLT is commonly used for one-lung ventilation (OLV) and lung separation during thoracic surgery. Compared to SLT, DLTs have a larger outer diameter and are made of a stiffer catheter material, making them more susceptible to postoperative complications such as airway injury. In addition, DLT often requires frequent maneuvering and repositioning to achieve optimal one-lung ventilation, and changes in thoracic surgical positioning can lead to friction between the DLT and the airway, resulting in airway injury. Furthermore, the preformed curve of the DLT may also lead to laryngeal injury during surgery and tracheal extubation.

The susceptibility factor for the development of posterior vocal fold granulomas is anatomical because the posterior vocal folds are structurally positioned close to the cricopharyngeal inlet and because their respiratory epithelium provides a lesser degree of protection compared to the squamous epithelium of the vibrating vocal folds, the posterior vocal folds are more susceptible to additional chemical irritation caused by non-acidic or (and) acidic laryngopharyngeal reflux, which can injure the laryngeal mucosa, as well as the cartilaginous portion of the vocal folds. When this irritation persists, the mucosal damage is prolonged and prone to recurrent granulomas. In addition, the mucosa on the surface of the vocal folds is thin, and habitual clearing of the voice, coughing, and vocal fold abuse result in too frequent collisions between the arytenoid cartilages bilaterally, which can easily damage the mucosa and lead to the formation of ulcers, and then granulomas can form under the stimulation of localized inflammation. These factors do not exist independently of each other, and the incidence of granulomas is greatly increased when multiple factors coexist.

The clinical symptoms of VPGs are mainly hoarseness, the degree of which is related to the size of the polyp and the site of growth. Small polyps or limited polyps on the surface of the vocal folds have only slight voice changes, but the initial damage may lead to permanent voice damage; polyps with a broad base and located at the free edge of the vocal folds have more severe hoarseness, which is often manifested by difficulty in making a sound, pharyngeal sensation of a foreign body, coughing, and in more severe cases, the vocal folds may be obstructed by vocal folds, thus causing inspiratory laryngeal wheezing and dyspnea. More severe cases can be caused by vocal polyps obstructing the vocal folds, thus causing inspiratory laryngeal stridor and dyspnea. In some cases, IGs are asymptomatic and are detected during laryngoscopy for other laryngeal diseases. At the

same time, IGs may also have different clinical features from CGs due to factors affecting the pathogenesis of IGs, including physical and direct factors, such as pressure necrosis of the epiglottis mucosa induced during intubation maintenance or arytenoid cartilage mucosal scraping injuries that may occur during tracheal intubation, and postoperative patients may have symptoms such as a sore throat or painful swallowing. However, because VPGs are a rare disease, there is no consensus or guidelines for their treatment, and various treatments are mainly based on physicians' preferences. According to a recent meta-analysis of IGs treatments, it has been suggested that recommended treatments for IGs include anti-reflux therapy, speech therapy, local injection of botulinum toxin (BTX), zinc sulfate, antibiotics, oral steroid inhalers (SIs), mitomycin C, and operation [15]. It has been suggested that the treatment of CGs and IGs is similar, with the treatment of CGs being based on conservative vocal therapy (which may include vocal rest and speech therapy), along with the treatment of any potential predisposing causes (e.g., gastroesophageal reflux, etc.). However, according to recent findings, the CGs and IGs groups responded differently to combined drug therapy, with the IGs group responding better to combined PPI and SI therapy than the CGs group [16]. There may be three reasons for this result. First, the combination therapy of PPI and SI is expected to treat VPGs through two different mechanisms: PPI inhibits the mucosal damage of the vocal folds caused by gastric acid reflux, and SI reduces the localized inflammation of the vocal folds. Second, the tracheal intubation that directly induced physical irritation in the IGs group was temporary, and this causative factor was eliminated during the treatment. Further, the IGs group may have been inherently more capable of self-healing than the CGs group, with a shorter healing time. When the combination of PPI and SI is ineffective, local injection of BTX is another good option for some refractory glottic granulomas [17]. BTX weakens the laryngeal musculature, thus preventing the glottis from closing entirely and avoiding contact with the contralateral arytenoid cartilage, which may reduce the number of repetitive traumas. However, one should be alerted to the presence of the risk of hoarseness of the voice or difficulty in swallowing, especially in vocal professionals, who should be carefully selected and informed of the risks. However, although it seems that in patients with IGs, conservative treatment can be curative, the reality is that most clinical patients cannot tolerate the extraordinarily long treatment period (6 months) and opt for direct surgical treatment. Surgical excision is a good treatment option when medication fails, the lesion is pedunculated, or causes dyspnea. In this case, the patient had a massive granuloma of the vocal folds that had obstructed the airway and caused respiratory distress. In addition, a difficult airway was present at the time of induction of re-anesthesia, and surgical treatment was the best option.

Our patient had no history of gastroesophageal reflux, and her job did not require excessive vocalization, and she had no recent history of upper respiratory tract infection. Therefore, vocal cord injury is more likely to occur during sur-

gery than before. Typically, the choice of DLT size depends on the patient's gender and height, and the following is recommended: 39 Fr DLT for men > 178 cm; 37 Fr DLT for men 160 - 178 cm and women > 165 cm; 35 Fr DLT for men ≤ 160 cm and women 153 - 165 cm; 32 Fr DLT for female patients ≤ 153 cm in height [18]. In this case, we used a 35 Fr DLT with a tube depth of 26 cm. The tube diameter was selected reasonably according to the patient's height, and the tube was positioned using an electronic flexible scope with good alignment. 26 cm was not deep [19], and the patient awoke smoothly without choking. The most likely reason for the factors associated with the formation of vocal granuloma in this patient is that the patient was lying on the right side during the operation, and the double-lumen bronchial catheter just compressed the right vocal cord below, leading to local ischemia and mechanical damage on the right side. In addition, it is also considered that in this case, when the patient was lying on the right side, the reflux fluid of gastric contents and oral secretions flowed along the underside of the catheter and accumulated near the vocal folds on the right side below, which further stimulated the compressed vocal folds. Possible factors include frictional damage to the laryngeal and/or tracheal mucosal epithelium from catheter movement during intubation or (and) during intraoperative position changes, as well as the long duration of catheterization (140 minutes). It may also be due to excessive pressure on the catheter sleeve. The pressure of the catheter sleeve, which is usually estimated by palpation based on personal experience, is often much higher than the measured or optimal value [20], and it is hoped that tracheal catheters with pressure monitoring devices or self-limiting sleeve pressures can be invented in the future. Moreover, the postoperative follow-up is insufficient to detect and treat the lesion in time, which leads to the deterioration of the lesion.

So, how can we prevent and control the occurrence of medical-induced membranous vocal fold granuloma? For patients with a high risk of granuloma, before anesthesia, should pay attention to asking about their risk factors, such as whether there is a history of gastroesophageal or pharyngeal reflux, whether there is a history of general anesthesia surgery, whether long-term excessive use of voice and excessive cleaning of the throat, whether chronic cough, etc., a complete understanding of the medical history and proficiency in understanding the anatomical structure of the vocal folds. When choosing the appropriate model of the double-lumen bronchial catheter for patients under general anesthesia, the appropriate tracheal catheter for the patient should be carefully selected so that experienced anesthesiologists can operate gently to avoid unnecessary damage. At the same time, if conditions permit, for patients prone to postintubation vocal fold granulomas, measure the proportion of the vocal folds on their chest radiographs and carefully choose the appropriate catheter model. In this case, no laryngeal CT was taken before the first operation, which was also our shortcoming. Some scholars have shown in clinical trials that thermal softening of the DLT before intubation also seems to help reduce the airway injury associated

with DLT intubation [21]. Alternatively, placing the DLT with the patient in the supine position, without a headrest, can also minimize catheter migration in lateral recumbency and reduce damage from friction on the airway [22]. In clinical practice, anesthesiologists fix the oral tracheal tube in one corner of the mouth to leave more space for the surgeon to operate the oropharyngeal surgery and to connect the respiratory circuit of the anesthesia machine more conveniently or in the course of the surgery, the mid-oral tracheal tube unconsciously shifts to the corner of one side of the mouth and is discovered later. It exerts tremendous pressure on one side of the vocal folds and easily causes laryngeal injuries, thus leading to laryngeal mucous membrane ulceration and inflammation, which can lead to ulceration and inflammation of the laryngeal mucosa, followed by granuloma formation. Therefore, it is recommended that the tracheal tube be placed in the midline to avoid overstimulation of one side of the glottis and that local medication be given to the glottis before intubation to reduce inflammation. For surgeries that require the tracheal tube to be fixed on the corner of the mouth or for very long surgeries, it is recommended to ensure adequate catheter sleeve pressure (between 20 to 30 mm Hg), avoiding extreme pressures (>30 mm Hg), and manually deflating the catheter sleeve by the anesthesiologist at regular intervals, to give the valve tissue time to breathe and to prevent ischemic necrosis. The anesthesiologist must also ensure that the patient is adequately sedated and/or muscle relaxed during anesthetic intubation, extubation, or surgical manipulation. This is because the movement of the patient's neck causes the catheter to move within the airway. The patient's involuntary swallowing and headshaking motions can push the catheter to the side of the vocal cords, resulting in friction between the tube and the laryngeal and tracheal mucosal epithelium, which can compress or injure the surface epithelium of the vocal cord elevations. Finally, it is also necessary to prevent postoperative nausea and vomiting from occurring, especially in female patients, following the combination of drugs, drugs that inhibit gastric acid secretion, anticholinergics to reduce secretion, and timely oral suctioning to prevent postoperative reflux of gastric contents to stimulate the laryngeal mucosa and exacerbate intubation laryngeal injury.

In summary, during general anesthesia intubation, it is necessary to carefully and actively avoid the occurrence of rare post-intubation complications by using appropriate intubation protocols and tracheal tube sizes, adequate sedation, avoiding laryngeal injuries during intubation and after extubation, and attracting oral secretions promptly, to ensure that the patient's perioperative period is safe and smooth.

Acknowledgements

Not applicable.

Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Committee of The First Affiliated

Hospital of Yangtze University to be conducted.

Consent for Publication

Written informed consent to publish the clinical details and images of the patient was obtained.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

There are no competing interests.

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Authors' Contributions

XQ Zeng and XY Xi collected the literature and wrote the manuscript. S Guo, Y Zhao, and B Li revised the manuscript. R, Xia designed, wrote, edited, and prepared the manuscript for submission. All authors read and approved the final manuscript. XQ Zeng and XY Xi contribute equally to this work.

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Abbreviations

DLT, Double-Lumen Endotracheal; SLT, Single-Lumen Endotracheal; VPGs, Vocal Process Granulomas; CT, Computed Tomography; IGs, Intubation Granulomas; CGs, Contact Granulomas; TEM, Transmission Electron Microscope; OLV, One-Lung Ventilation; BTX, Botulinum Toxin; SIs, Steroid Inhalers.