Consequences of Intubation in COVID-19 Patients: Are We Ready?

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ABSTRACT

Aim and objective: We report a case of a 61-year-old man, still recovering from COVID-19, who developed acute respiratory distress syndrome (ARDS) requiring hospitalization and intubation in early March 2020. Consequently, he developed post-intubation bilateral massive vocal fold granulomas. To date, this is the first case report of laryngeal granulomas following intubation since the outbreak.

Background: Clinical presentation of COVID-19 ranges from being asymptomatic to mild symptoms while a fraction of them develop ARDS. There is a need to highlight the probability of a rise in the number of patients with complaints of voice change and laryngeal lesions in the coming months. More specifically, post-intubation laryngeal granulomas.

Case description: The patient timeline, blood exams, serological tests, radiological examination, voice evaluation, and videolaryngoscopy of a 61-year-old recovered COVID-19 patient with bilateral vocal fold granulomas have been described in detail that would assist in clinical decision-making.

Conclusion: A significant number of patients underwent intubation at the beginning of the pandemic. These patients can be expected to be frequent visitors at the outpatient clinic and emergency rooms in the future with complaints of change in voice and laryngeal lesions. The question of whether we are ready for it needs to be assessed.

Clinical significance: Patients who underwent long-term intubation following ARDS after contracting COVID-19 infection need to be further evaluated and kept on a regular follow-up.

Conclusion: Information regarding intubation granuloma risk, breathing exercises, and speech therapy might be beneficial to such patients. We need to be well prepared to expect a surge in the number of cases reporting with voice disorders shortly.

Keywords: Benign vocal fold lesions, Dysphonia, Endotracheal intubation, Granulom, Speech therapy, Vocal fold, Voice analysis, Voice disorders.

BACKGROUND

The COVID-19 pandemic has led to over 74 million diagnosed cases and over 1 million deaths across the globe.1 The clinical presentation of patients with COVID-19 ranges from being asymptomatic to experiencing mild symptoms while a fraction of them develop acute respiratory distress syndrome (ARDS) requiring intubation and invasive ventilation at some point in their disease course. An improved understanding of COVID-19 pathogenesis has re-assessed invasive ventilation from “need of the hour” previously to “the last resort” now.2 Although previous studies3 have discussed the development of laryngeal lesions following intubation, it necessitates special focus owing to the current global scenario. This is where we need to highlight the probability of a rise in the number of patients with a change in voice and laryngeal lesions in the coming months. More specifically, post-intubation laryngeal granulomas. These are benign lesions presenting predominantly between the fourth-fifth decades of life, uni- or bilaterally as sessile or pedunculated masses involving the posterior third of the vocal folds, the vocal processes, or the arytenoids. They represent a “repairing, reactive inflammatory process” of the mucosa, usually secondary to local injury. The etiology is multifactorial: vocal abuse (33%), traumatic or prolonged endotracheal intubation (23%), gastroesophageal reflux (30%), or idiopathic.3 We report a case of a patient recovering from COVID-19, who had developed ARDS requiring hospitalization and intubation. Consequently, he presented with massive post-intubation bilateral vocal fold contact granulomas. To date, this is the first case report of laryngeal granulomas following intubation since the outbreak. In addition to this, wearing masks and shields might contribute to the vocal strain increasing the probability of vocal fold lesions.

CASE DESCRIPTION

A 61-year-old man recovering from COVID-19 with a history of hospitalization and intubation visited the outpatient clinic on request by an ENT specialist who noticed the patient’s hoarse
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**Figs 1A and B:** The patient timeline from the onset of first symptoms, hospitalization (day 0), intubation (day 3), extubation (day 21), and presentation with hoarseness is described in (A). The laboratory exams, blood exams on admission, hospitalization, and at follow-up along with serology for antibody titers are tabulated in (B).

### Table: Laboratory Exams

| Variable                      | Reference Range | On Admission Day 0 | Hospital Day 9 | Hospital Day 33 | At follow-up |
|-------------------------------|-----------------|--------------------|----------------|-----------------|--------------|
| **Blood**                     |                 |                    |                |                 |              |
| Hematocrit (%)                | 40-52           | 36.8               | 40.1           | 35.2            | 36.5         | 37.7         |
| Hemoglobin (g/dL)             | 13-17           | 13                 | 13.4           | 12.1            | 12           | 12.5         |
| RBC count (×10⁹ per µL)       | 4.5-5.8         | 4.46               | 4.57           | 4.18            | 4.02         | 4.19         |
| White cells (×10³ per µl)     | 4-10            | 6.35               | 4.2            | 6.78            | 6.88         | 7.41         |
| **Differential Count**        |                 |                    |                |                 |              |
| Neutrophils (%)               | 40-74           | 88                 | 88.7           | 65.1            | 62.4         | 58.9         |
| Lymphocytes (%)               | 19-45           | 8.7                | 5.8            | 22.9            | 29.3         | 33.2         |
| Monocytes (%)                 | 2-10            | 2.1                | 4.0            | 9               | 7.5          | 7            |
| Eosinophils (%)               | 0.5-5           | 0                  | 0.2            | 0.3             | 0.5          | 0.5          |
| **Coagulation profile**       |                 |                    |                |                 |              |
| Platelets (×10³ per µl)       | 120-450         | 97                 | 154            | 220             | 173          | 158          |
| Prothrombin time (sec)        | 12-13           | 12.1               | 12.5           | -               | -            | -            |
| Partial thromboplastin time (sec)| 24-35    | 28                 | 22             | -               | -            | -            |
| INR                           | 0.8-1.1         | 1.1                | 1.1            | 1.1             | 1.1          | 1.1          |
| Fibrinogen (mg/dL)            | 150-450         | 581                | 404            | -               | -            | -            |
| D-dimer (µg/mL)               | 0.4-4           | -                  | -              | 1.4             | -            | -            |
| **Electrolytes**              |                 |                    |                |                 |              |
| Sodium (mmol/L)               | 135-148         | 132                | 141            | 137             | -            | -            |
| Potassium (mmol/L)            | 3.5-5.3         | 3.6                | 5.2            | 4.2             | -            | -            |
| Chloride (mmol/L)             | 98-106          | 100                | 101            | 99              | -            | -            |
| Calcium (mmol/L)              | 1.15-1.35       | 1.04               | 1.25           | 1.32            | -            | -            |
| Total Protein (g/dL)          | 6.1-7.9         | 5.5                | 5.3            | -               | -            | -            |
| Albumin (g/dL)                | 3.5-5.2         | 2.2                | 1.9            | -               | -            | -            |
| **Liver enzymes**             |                 |                    |                |                 |              |
| SGOT (U/L)                    | 0-40            | 38                 | 68             | 22              | 20           | 22           |
| SGPT (U/L)                    | 17-63           | 28                 | 145            | 64              | 38           | 39           |
| GGTP (U/L)                    | <55             | 14                 | 20             | 23              | 17           | 17           |
| **Arterial Blood Gas Analysis**|                 |                    |                |                 |              |
| pH                            | 7.37-7.45       | 7.39               | 7.3            | 7.37            | -            | -            |
| pCO₂ (mm Hg)                  | 35-46           | 50.0               | 49             | 44              | -            | -            |
| pO₂ (mm Hg)                   | 75-100          | 69.0               | 74             | 92              | -            | -            |
| HCO₃⁻ (mmol/L)                | 21-28           | 30.3               | 29             | 27              | -            | -            |
| Anion gap (mmol/L)            | 4-17            | 5.0                | 6              | 7               | -            | -            |
| BE (mmol/L)                   | -2.0 - 3.0      | 4.2                | 4.8            | 2.7             | -            | -            |
| CRP (mg/dL)                   | 0.1-0.7         | 2.64               | 0.73           | <0.1            | 0.02         | 0.01         |
| Ferritin (ng/mL)              | 22-322          | -                  | 1264           | 646.40          | -            | -            |
| LDH (U/L)                     | 266-500         | 841                | 666            | 530             | -            | -            |
| **Antibody Titre by ELISA method** |             |                    |                |                 |              |
| SARS-CoV-2 IgG                | Non-reactive 9   | 1.73               | 25.46          | -               | -            | -            |
| SARS-CoV-2 IgM                | Reactive >11   | 1.0                | 1.49           | -               | -            | -            |

Two different methodologies, ELISA and CLIA, were used to assess the IgG and IgM antibody levels. The IgG was reactive at 11 weeks (+3 months) after the first positive swab and at 6.7 weeks (+1 month) after negative swab.
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Voice during a telephonic conversation. Since the ENT specialist had himself recovered from COVID-19 infection a month ago, he further questioned the patient about his first symptoms before and after hospitalization, i.e., anosmia, ageusia, fever (38.8°C) shortness of breath, and fatigue. Past history revealed hypertension, dyslipidemia, angioplasty, and benign prostate hypertrophy. The patient was allergic to amoxicillin, was a former smoker, and had quit 20 years prior. Detailed verbal history and medical record analysis revealed intubation for 18 days at the hospital following ARDS after testing positive for the novel coronavirus. Additionally, at the time, due to the unavailability of propofol, midazolam was administered for superficial sedation. Intubation was performed using a cuffed endotracheal tube (ETT) of 8 mm internal diameter, in a single attempt with direct laryngoscopy. He was extubated successfully but developed hoarseness of voice after 4 days, gradually progressive in nature. Keeping the history in mind, an appointment was scheduled for serology as well as laryngoscopy. The patient timeline from the onset of first symptoms, hospitalization (day 0), intubation (day 3), extubation (day 21), and presentation with hoarseness is described (Fig. 1A) with lab exams (Fig. 1B). Treatment protocol during hospitalization involved respiratory support, lopinavir, ritonavir, chloroquine, and a cover of steroids. At the appointment, the patient was afebrile with a blood pressure of 138/88 mm Hg, respiratory rate of 30/minute, and oxygen saturation maintained at 98% on ambient air. He was on chest physiotherapy, with a complaint of progressive hoarseness of voice and mild difficulty in breathing. On general conversation and routine examination, a hoarse raspy voice with moderate roughness

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**Figs 2A and B:** Voice analysis using VHI-10, MPT, and the GRBAS scale described in (A). Flexible videolaryngoscopy (B, i) reveals bilateral vocal fold granulomas with contact lesion (*), epiglottis (e), and the vocal folds (dotted lines); patient undergoing blood exam and serological tests (B, ii); patient chest radiographs (B, iii)
was noted. The patient had a high Voice Handicap Index-10 (VHI-10) of 26, low maximum phonation time (MPT) of 12 seconds, and a GRBAS (grade, roughness, breathiness, asthenia, strain) scale of 7. Flexible videolaryngoscopy revealed around 1 × 1.5 cm sized, well-defined nodular-polypoidal lesions arising from bilateral aryepiglottic folds blocking the posterior laryngeal inlet significantly, impinging on to the arytenoids, and compressing them. A contact lesion was noted (Fig. 2B). As per the endoscopic grading system, the granulomas in this patient were of grade 4B.

**Discussion**

Prolonged intubation is one of the most common causes of laryngeal granuloma. Additionally, laryngeal trauma could be due to an “extremely large-sized tube, abnormal position of the patient’s head and larynx, superficial sedation, misplaced or tube cuff overpressure, and extubation trauma, further contributing to granuloma development”. Intubated patients have the cannula positioned in the posterior cartilaginous glottis between the vocal processes of the arytenoid cartilages. The arytenoids are covered by a thin-layered perichondrium and mucosa, making them susceptible to trauma. Upper respiratory tract infections and excessive coughing preceding pneumonia might play a contributory role in granuloma development. The movements of the vocal folds and trachea are equally important determinants. Spontaneous ventilation causes the vocal folds to adduct-abduct-constrict passively shorten with each inspiration-expiration cycle. However, with controlled respiration, the ETT moves along its longitudinal axis causing an ETT rub against the tracheal surface further predisposing to granulomas. Treatment options include vocal hygiene, treating allergies/Gastroesophageal reflux disease (GERD), steroids (systemic/intralesional), and eventually, laryngeal surgery using cold knife instruments/laser (microscope-assisted/endolaryngeal surgery). Although anesthesiologists consider hoarseness to be a common post-intubation complication, it needs vigilant observation and a strict follow-up.

**Conclusion**

As otolaryngologists, we need to predict and prepare for a probability of a rise in the number of patients with laryngeal lesions in the coming months. This is the first case report of post-intubation massive bilateral laryngeal granulomas since the outbreak. The clinical presentation of patients with COVID-19 ranges from being asymptomatic to experiencing mild symptoms while a fraction of them develop ARDS requiring intubation and invasive ventilation at some point in their disease course. During the initial few months, a considerable number of patients were intubated. An improved understanding of COVID-19 pathogenesis has re-assessed invasive ventilation from “need of the hour” previously to “the last resort” now.

**Clinical Significance**

Points to note before discharging patients

- Patients should be informed of the risk of intubation granulomas and their symptoms so that during recovery if they develop new/sustained hoarseness they should visit the clinic for assessment.
- Role of transcutaneous laryngeal ultrasound in place of flexible fiberoptic laryngoscopy: provides “rapid noninvasive assessment of the vocal fold function” assisting in clinical decision-making along with early identification of any vocal fold issue that might eventually help avoid an emergency reintubation.
- Laryngoscopy before discharge is recommended, as it could indeed help us identify any early signs of granuloma formation/edema. However, with the ongoing pandemic, there are uncertainties regarding the viral shedding and infectivity status in COVID-19 recovered patients and hence this requires further studies.
- Speech therapy and breathing exercises should be advised for all patients, especially the long haulers (patients experiencing symptoms for longer duration).
- Oxygen saturation cannot be confirmatory evidence of wellbeing. Using a pulse oximeter at home should be recommended.

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