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BRIEF COMMUNICATION

Laryngotracheal Stenoses Post-Acute Respiratory Distress Syndrome due to COVID-19: Clinical Presentation, Histopathological Findings and Management. A Series of 12 Cases

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Abstract Coronavirus disease 2019 (COVID-19) has increased the risk of developing severe acute respiratory distress syndrome and subsequent moderate to severe laryngotracheal stenoses (LSTs) with an early presentation that occurs between two and three months after SARS-CoV-2 infection. We present a series of 12 cases of LST following SARS-CoV-2 infection. Dense lymphocyte infiltration with multinuclear giant cell granulomas was found on biopsy with intranuclear inclusions, suggestive of viral cytopathic effects in one case and intravascular fibrin thrombi with perivascular mononuclear infiltrate of CD3 + T lymphocytes. We present the largest and only series that describes clinical and histopathological characteristics of LTS and the management and outcomes after early laryngotracheal reconstruction in the context of the SARS-CoV-2 outbreak.

Keywords COVID-19 · Histopathology · SARS-CoV-2 · Laryngotracheal stenosis · Subglottic tracheal stenosis

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Introduction

In December 2019, the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presented with pneumonia of an unknown origin in Wuhan (Hubei, China). In January 2020, the viral genome of SARS-CoV-2 was sequenced, and this particular alignment was then termed coronavirus disease 2019 [1]. In March 2020, the infection was declared a global pandemic [1]. The pandemic has been challenging, and one of the nascent consequences of it has been the early presentation of laryngotracheal stenosis (LTS), which is a debilitating and potentially life-threatening condition that is commonly caused by iatrogenic events as a result of endotracheal intubation or tracheostomy. The percentages of LTS seem, until now, higher and to have a preponderance for the subglottic area. It is known that the pathological mechanisms of this disorder involve ischemia and scar formation, which leads to narrowing of the airway and disturbances in its patency [2]. Current data demonstrated that approximately 9.8 to 15.2% of patients required invasive mechanical ventilation (IMV) [1], and it is estimated that the median duration of ventilation is approximately 17 days, and patients undergo a high rate of reintubation. Additionally, due to the increase in IMV use and the prolongation of ventilation, patients during the pandemic have been subjected to overcuffed intubation, prone position ventilation and overinflation of an endotracheal tube cuff to avoid aerosol sprays and the movement of the tube in the prone position. All of these factors and patient comorbidities might contribute to the mechanism underlying stenosis[2].

Currently, it is known that temporary Montgomery T--tube placement and tracheostomy are no longer considered possible alternatives because of the risk of bacterial

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colonization and extension of the stenotic segment, which usually represent a last resort. For that reason, surgical resection and tracheal reconstruction are the definitive treatments of choice [3]. However, the management of LTS is still controversial during the pandemic due to the risk of the contamination of healthcare workers and lack of information on this pathology after SARS-CoV-2 infection. The few cases reported in the literature have been mostly managed by endoscopy balloon dilatation and eventual intralesional corticosteroid injection [2, 4] or definitive tracheostomy. The rate of tracheostomy after SARS-CoV-2 is still unknown.

The available evidence suggests that SARS-CoV-2 compromises organs via microvasculitis changes and dense lymphocyte infiltration with multinuclear giant cell granulomas. In the trachea, it has been possible to identify intranuclear inclusions suggestive of viral cytopathic effects [5, 6]. Current literature of retrospective studies demonstrated that almost half of patients with SARS-CoV2 developed full-thickness tracheal lesion and/or tracheoesophageal fistulas after prolonged IMV [7]. For that reason, a high level of suspicion for LTS development should be maintaining [8]. We present a series of 12 patients with LTS after SARS-CoV-2 infection managed by early surgical resection and tracheal reconstruction.

Case Series

In a series of 12 cases of LTS post-SARS-CoV-2 infection, the average age of the patients was 59.7 years old (Interquartile range (IQR) 57–67) and included 4 females and 8 males, 2 of whom had undergone tracheostomy prior to acute respiratory distress syndrome (ARDS). The majority of the population had hypertension (Table 1). Patients presented signs of airway obstruction approximately 64 days (IQR 30–125) after SARS-CoV-2 infection and had clinical presentations that were more severe than other cases of LTS due to the complexity of the stenotic airway tract (length 3.5 cm (IQR 3 -4) with an average 69% stenotic area) (Fig. 1). For this reason, 7 patients underwent laryngotracheal reconstruction (LTR) after 77 days (IQR 58–103 days) of positive SARS-CoV2 PCR results. Ten patients were decannulated, and any complications presented during or after the procedure. One patient died before the procedure due to multiple comorbidities. Other characteristics of the population, the stenotic airway tract and pathology are described in Table 1.

Pathological Examination

Macroscopic and Microscopic Findings

LTS samples showed small bleeding areas and thickened mucosa in the cartilaginous area. On microscopic examination, the mucosal sample displayed large areas of partial erosion of the epithelium and patchy coagulative necrosis, and in 2 cases, the necrosis extended from the mucosa to the stroma (Table 1 and Fig. 2C). All the samples presented extensive lymphocytic inflammatory infiltrate (Fig. 2) that was interstitial, perivascular and periglandular. Microvasculitis and fibrin microthrombi were observed in the vessels (Table 1 and Fig. 2). The presence of acute inflammation associated with granulation tissue was visible in the superficial layer of the epithelium in the whole series (Fig. 3). Some foci of granulocytic inflammation were also detected that were formed by multinucleated giant cells (Fig. 3D-E). Immunohistochemistry using CD3 and CD4 monoclonal antibodies was performed to characterize the lymphomonocytic infiltrate, which showed perivascular lymphocyte infiltration and the disruption of vessels by lymphocytic microvasculitis (highlighted with CD34) (Fig. 4A-B). Additionally, cells with suspected cytopathic viral effects were detected in one patient (Fig. 4C), although this finding was not confirmed by immunohistochemistry.

Discussion

Posttracheotomy stenosis involving the cricoid cartilage is becoming more frequent and generating more challenging scenarios for repairing airway patency [5, 6]. The reason for this increase in the frequency of high airway lesions is unclear, but it has been hypothesized that the placement of tracheotomy in difficult circumstances or severe inflammation of the airway, as is seen in SARS-CoV-2 patients, might contribute to the increase [6]. A different hypothesis has been suggested to explain the pathological mechanisms in LTS post SARS-CoV2 infection that posits that different factors might play a role, such as positive-pressure ventilation, delayed tracheotomy, prone positioning and the overinflation of an endotracheal tube cuff to avoid aerosol sprays, leading to subsequent inflammation of the airway with vasculitis phenomena, increasing the rate of tracheal injuries and generating fibrin microthrombi and lymphocyte microvasculitis (Figs. 2 and 3). Based on Minonisihi and Kim et. al, after change from supine to prone tracheal intubation, 91.7% patients had endotracheal tube (ETT) displacement. From those, 48% of the patients with EET moved more than 10 mm, whether 86.3% patients had

Table 1 Clinical and anatomopathological characteristics of LTS patients

Characteristic of the patients (n = 12)	
Sex	
Female	4 (33,3%)
Male	8 (66.6%)
Age	59,7 (57–67)
ASA	
II	2 (16.6%)
III	9 (75%)
IV	1 (8.3%)
Comorbidities	
Hypertension	9 (75%)
Diabetes mellitus	6 (50%)
Chronic kidney disease	2 (17%)
Heart disease	2 (17%)
None	1 (8%)
Duration of invasive mechanical ventilation	20 (16–26,5)
Time to stenoses after SARS-CoV-2 symptoms (days)	64 (30–105)
Stenosis characteristics (n = 12)	
McCaffrey Scale	
II	8 (66.6%)
III	2 (16.6%)
IV	2 (16.6%)
Cotton Meyer Scale	
I	4 (33.3%)
II	8(66.6%)
Previous tracheostomy	2 (16.6%)
Laryngotracheal resection	9 (75%)
Decannulation	10 (83%)
Pathology characteristics (n = 9)*	
Cytopathic effects (CPEs)	1 (11.1%)
Microvasculitis	5 (55.5%)
Perivascular lymphocytic infiltrate	
Mild	1 (11.1%)
Moderate	5 (55.5%)
Severe	3 (33.3%)
Interstitial Infiltrate	
Mild	1 (11.1%)
Moderate	5 (55.5%)
Severe	3 (33.3%)
Neutrophil Infiltration	
Mild	4 (44.4%)
Moderate	2 (22.2%)
Severe	3 (33.3%)
Granuloma	4 (44.4%)
Microthrombus formation (intravascular fibrin deposition)	3 (33.3%)
Fibrosis	8 (88.8%)
Necrosis	
Mild	6 (66.6%)
Moderate	2 (22.2%)

Table 1

Severe	1 (11.1%)
Granulation tissue	8 (88.8%)

*(n = 9) are the patient's that underwent to LT reconstruction

The table describes the clinical characteristics of patients who presented with LTS post-ARDS due to COVID-19 and describes the stenosis characteristics and pathological findings post-laryngotracheal reconstruction

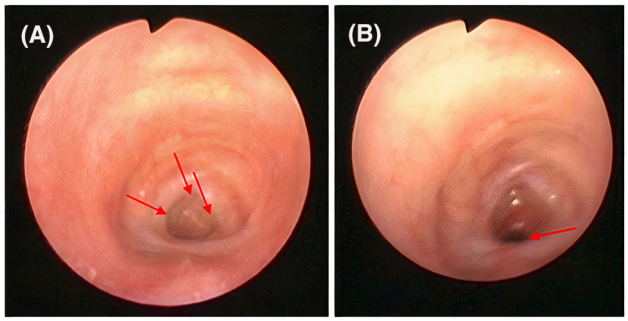

Fig. 1 Endoscopic and computed tomography (CT) scan of the neck. A and B show the endoscopic and CT scan of the stenotic tract, and yellow arrows indicate the stenotic area

changes in tube cuff pressure. Those with slight ETT movement had slight significant correlation in change of cuff pressure [9, 10].

The pandemic has posed challenges for all aspects of medicine, but a critical challenge is that the surgical management of LTS involving opening the airway creates a high-risk situation for all healthcare workers involved in management (surgeons, anesthesiologists and operating room personnel) [4]. Currently, there is not enough experience in the management of LTS and the pathological cascade in patients with LTS post-SARS-CoV-2 infection. This study aimed to increase the amount of evidence around LTS post-COVID-19 and describe changes in the

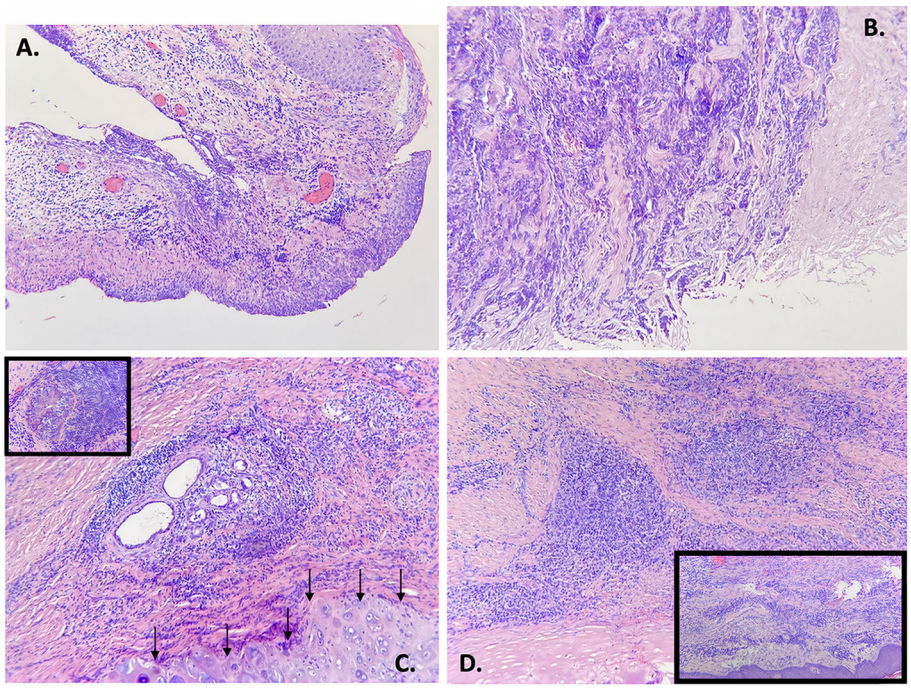

Fig. 2 Hematoxylin and eosin staining of the LTS specimens. A. Superficial coagulative necrosis with dense perivascular inflammatory infiltrate and the neoangiogenesis of submucosal tissue (4x). B. Coagulative necrosis of the submucosal tissue (20x). C-D. Intense lymphocytic perivascular infiltrate (10x). C. Periglandular inflammatory infiltrate (10x); the top left corner shows a higher magnification of the dense lymphocytic infiltrate. The arrows show the cartilage of the airway surrounded by infiltrate. D. Dense inflammatory interstitial infiltrate; a lower magnification is shown in the bottom right corner, which shows the infiltrate in the different layers of the specimen up to the submucosa

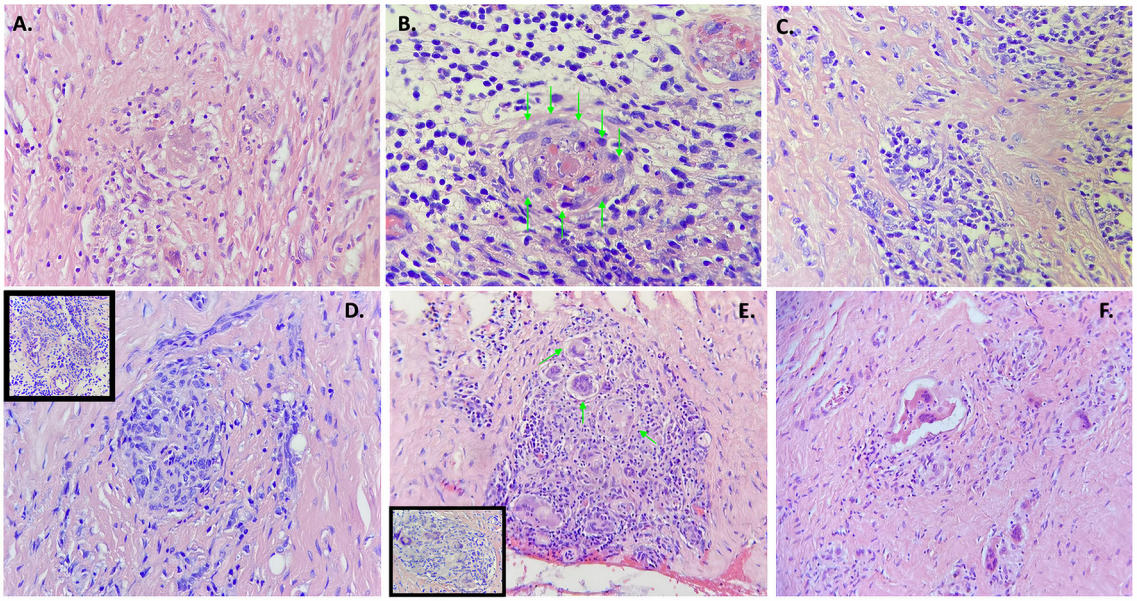

Fig. 3 Small vessels changes. A-B. Microvascular thrombosis (20x). A. Inflammatory infiltrate with extensive vessel microthrombi. B. Intravascular hemorrhagic thrombosis. Green arrows indicate highlight intravascular fibrin microthrombi in small vessels (20x). C-D. Microvasculitis (20x) E. Inflammatory infiltrate including multinucleated giant cells forming an aggregation of macrophages with signs of chronic inflammation (10x), as shown in the left bottom corner, highlighting the multinucleated cells (20X). F. Proliferative and fibrotic tissue surrounding monocytic-like cells on a background of dense granulated tissue (10x)

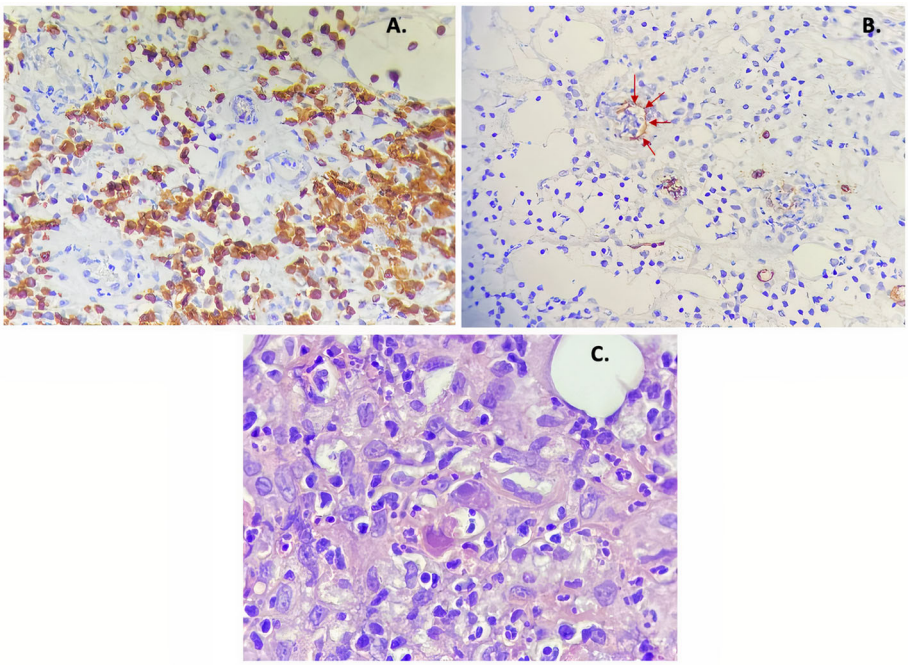

Fig. 4 Immunohistochemical staining with anti-CD3 and anti-CD34 antibodies and presumptive cytopathic viral changes. A. Dense perivascular lymphocytic infiltrate that is CD3 + . B. CD34 + staining highlights microvasculitis with vessel wall disruption (red arrows) and lymphocytes surrounding the perivasculature (10x). C. Suspected cytopathic viral changes (40x)

trachea after infection, which might influence the severity of stenoses. Additionally, we showed that it is possible to perform LTR in the early stenotic phase with an immature scar and post-ARDS due to COVID-19 should be considered for definitive surgical intervention to minimize complications and optimize long-term outcomes. This series demonstrated satisfactory appropriate outcomes of early LTS intervention without mortality or complications [11]. The reasons why we decided to perform LTR were a severe presentation of stenoses in the majority of McCaffrey II patients (73%) and 1 patient with a complex lesion. Other management strategies were not indicated due to the high

risk of mortality, and LTR was the gold standard. A current retrospective cohort study evaluating the difference between early intervention defined as procedure performed less than 45 days after intubation versus LTR performed greater than 45 days after intubation in a heterogenous group shows an absolute difference of decannulation rate of 32%, (95% CI, − 3% to 68%), those who received early treatment required fewer intervention compared to those with mature LTS (2.2 vs 11.5; absolute difference, 9.3; 95% CI, 6.4–12.1). This study suggests that early intervention of postintubation LTS might be associated with a decrease in tracheostomy-dependency rate, higher decannulation rate and lower procedure rate [11].

Furthermore, the histopathology of the LTS area allowed us to describe the SARS-CoV-2 tracheal involvement, which includes superficial coagulative necrosis with dense perivascular infiltrate, dense interstitial lymphocytic infiltrate, extensive vessel microthrombi and fibrin microthrombi, microvasculitis and giant cell aggregation with granulomas and suspected cytopathic viral changes. These findings have been previously described in other organs [5, 6], but little is known about SARS-CoV-2 impairment of the trachea.

Conclusion

The gold-standard procedure for LTS is surgical resection and reconstruction, and the principal cause of LTS is iatrogenic postintubation. Normally, surgeons delay management until the stenotic scar has completely matured and forms fibrotic tissue, which is after approximately 6 months. Histopathological characteristics are mainly characteristic of noncellular components and increased extracellular matrix (collagen) marked by fibrosis with mild chronic inflammation. Instead, patients with LTS post SARS-CoV-2 infection have relevant moderate to severe lymphocytic infiltrate, the presence of giant cells and severe necrotic microthrombi. For this reason, it is important to repair the stenotic area in the earliest period possible that does not pose occupational risk, which was 77 days (IQR 58–103 days). This guarantees excellent postoperative outcomes and a decannulation rate of 83% without complications.

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