Surviving COVID-19 and multiple complications post total laryngectomy

Arpana Singh,1 Abhishek Bhardwaj,2 Nivedhan Ravichandran,2 Manu Malhotra2

SUMMARY
The clinical manifestation of novel COVID-19 is variable. Pre-existing carcinoma and other comorbidities have been associated with increased COVID-19-related morbidity and mortality. Surgical intervention for advanced laryngeal carcinoma in old age during the COVID-19 pandemic may pose multiple challenges to the patient and the treatment team. We report a case of a 67-year-old elderly man who developed SARS-CoV-2 infection on the 21st day following total laryngectomy and neck dissection. The postoperative period was complicated by sequential development of pulmonary embolism, neck infection, pharyngeal leak and COVID-19 which were managed successfully. No close contacts were positive on the reverse transcription-PCR test for SARS-CoV-2. The patient is in follow-up for the past 7 months without any recurrence or COVID-19-related morbidity. The successful recovery and no cross-infection may be attributed to early diagnosis, immediate intervention and properly implemented institutional infection control policy.

BACKGROUND
COVID-19, first recognised in Wuhan, China, in December 2019, was determined by the WHO as a global pandemic.1 It is associated with rapid progression to severe acute respiratory distress, leading to intensive care.2 There are various risk factors like advanced age, comorbid conditions (heart, renal, liver and respiratory diseases), carcinoma, immune compression, smoking and pregnancy for acquiring severe COVID-19.3 Patients with carcinoma are in a state of immunosuppression, making them more susceptible to COVID-19-related complications and mortality.4 Moreover, most of the patients with laryngeal carcinoma have a chronic obstructive pulmonary disease component, which probably may accelerate the impact of COVID-19 infection on the airway.

CASE PRESENTATION
Preoperative
A 67-year-old male patient with difficulty swallowing for 1 month was diagnosed with moderately differentiated squamous cell carcinoma of the supraglottis, staged T4aN2cM0 based on radiology (figure 1). The patient had no history of substance abuse, contact with SARS-CoV-2-positive patient or any chronic illness. At admission, examination revealed body temperature of 98.6°F, blood pressure of 124/86 mm Hg, heart rate of 82 beats/min and respiratory rate of 16/min. The patient was anaemic with a haemoglobin of 11.2 g/dL. Other haematological parameters, chest X-ray findings and ECG findings were within normal limits. As per our institutional protocol to rule out false negativity for elective surgeries, the patient underwent testing of reverse transcription (RT)-PCR for SARS-CoV-2 twice before

Figure 1 Axial T1-weighted contrast images showing (A) bilateral cervical lymph nodes at level 2 and (B) right supraglottic growth invading thyroid cartilage.

In post total laryngectomy (TL), the alteration of airway physiology happens with the loss of nasal humidification and warming and mucociliary clearance, increasing the risk of severe respiratory disease.2 Also, as patients with laryngeal carcinoma are primarily elderly, the risk of acquiring a severe form of COVID-19 increases because comorbidities and ACE2 expression (increased expression associated with worse prognosis) increase with age.6 As per evidence, the risk of developing severe clinical events was higher in patients with cancer who concomitantly contracted COVID-19 after surgery.7

We report a successful recovery from COVID-19 in a case of a 67-year-old man who developed the infection, pulmonary embolism (PE), neck infection, and pharyngeal leak after undergoing TL and bilateral modified radical neck dissection (MRND) for stage IV supraglottic carcinoma.

Figure 2 Chest X-ray images on (A) day 6 showing blunting of bilateral costophrenic angle suggestive of pleural effusion and (B) day 20 showing resolution of earlier findings.
Case report

surgery: the first 72 hours before surgery and the second 24 hours before surgery. Both test results were negative.

Operative details
The patient underwent TL with partial pharyngectomy, bilateral MRND type V and pharyngeal reconstruction. The intraoperative period was uneventful. Postoperatively, the patient was kept on Ryle’s tube feed and started on broad-spectrum antibiotics, anti-inflammatory drugs, oral calcium and thyroxine supplementation. For a description of events, the day of surgery has been considered as day 1.

Development of PE
On day 6, the patient’s oxygen saturation (SpO₂) at room air dipped below 90%, and he was started on supplemental oxygen of 6 L/min. Chest X-ray (figure 2) revealed the possibility of pleural effusion, which was confirmed on ultrasound, revealing less than 10 mL collection on both sides; diagnostic pleural tap did neither reveal any malignant cell nor any microbe. As pleural effusion persisted until day 9, CT angiography was done, revealing embolus in the right main and left inferior pulmonary artery. Echocardiography was normal. The patient was started on injectable low-molecular-weight heparin (LMWH) 60 mg per day and oral ecosprin 75 mg per day on day 9. Oral ecosprin is continuing; LMWH continued until the day of discharge and was replaced with oral rivaroxaban 5 mg, which continued for 1 month.

Development of neck infection and pharyngeal leak
The patient developed gaping with slight blackening of neck incision wound on day 6, with the progression of neck flap necrosis consecutively and development of pharyngeal leak on day 10. Aseptic dressing of neck wound was done two times per day by residents in partial personal protective equipment (N95 mask, surgical gown and eye-protective goggles); healthy granulations developed on day 19 (figure 3).

Intensive care unit stay and the first episode of fever
As SpO₂ dipped to 80% with 8 L/min of oxygen on day 12, the patient was shifted to the intensive care ward. He was kept on synchronized intermittent mandatory ventilation for 36 hours, after which he was shifted back to the ward as his SpO₂ improved to 95% at room air.

On day 13, he developed fever that persisted for 2 days with a temperature ranging between 99°F and 101°F. Nasal, oropharyngeal and tracheal swabs were sent for SARS-CoV-2 testing, and reported as negative on day 15.

Diagnosed positive for SARS-CoV-2 infection
On day 20, the patient was stable with SpO₂ more than 96% on room air and healthy granulation in the neck wound bed. He was planned for flap reconstruction of the neck wound; hence as per the institutional protocol of a requirement of a negative report for SARS-CoV-2 infection before elective surgery, nasal, oropharyngeal and tracheal swabs were sent for RT-PCR. He was reported positive for the infection on day 21 with cycle threshold values 27/28 (targets—E/ORF1ab), suggesting a high viral load (figure 4). Blood examination showed monocytosis with neutrophilia and lymphopenia. Direct bilirubin and liver enzymes (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase) were increased. The patient was shifted to the COVID-19 isolation ward. During the period of isolation, there was no episode of fever, respiratory difficulty or oxygen desaturation below 90%. He was started on budesonide (1 mg) nebulisation 12 hourly. His oxygen saturation at room air fluctuated between 91% and 94%, and he was kept on high-flow oxygen (8–10 L/min), which maintained SpO₂ more than 96%. No anti-viral drug or systemic steroid was given to the patient.

All close contacts were screened for SARS-CoV-2 infection by RT-PCR and were negative. On day 26, a repeat nasopharyngeal swab of the patient was sent, which was reported as negative. Blood reports were normal (table 1).

Flap reconstruction and follow-up
The patient underwent primary closure of pharyngeal leak and reconstruction of neck wound using deltopectoral flap on day 28, which were successful.

Figure 3 Images showing (A) healthy granulation tissue in neck with a pharyngeal leak; (B) deltopectoral flap and split skin graft reconstruction of neck wound; (C) well-healed neck wound and donor left deltopectoral region after 2 months of reconstruction.
leucopenia were seen, which returned to normal levels on recovery (table 1).

Cancer is considered a risk factor for complications related to COVID-19 infection. In these patients, there is a higher risk of contracting the infection. They suffer from more severe disease course and increased risk of death, with a more significant proportion of such patients requiring higher levels of intensive care. In this context, it is essential to understand the factors that influence the outcome in patients with cancer.

Immunosuppression in cancer plays a vital role in the response and clinical outcomes of SARS-CoV-2 infection, although there is an unclear prognostic value. Immunosuppression could be a poor prognostic factor that may allow higher viral loads and increase secondary infection risk. Nutritional deterioration in patients with cancer leads to anaemia and hypoproteinaemia, which increases the susceptibility to respiratory pathogens as immunocompetence is affected. There is a higher risk of developing COVID-19-related severe clinical events in patients with cancer undergoing surgery. In our case, there was a state of prolonged immunosuppression, both cancer related and treatment induced. The patient was anaemic, for which he underwent multiple blood transfusions.

Patients with cancer, being common in the older age group, have more adverse outcomes of COVID-19 as ACE2 expression and comorbidities increase with age. SARS-CoV-2 acquired by respiratory aerosols binds to ACE2 receptors in the nasal epithelial

| Table 1  | Comparison of laboratory parameters of the patient during illness and after recovery from COVID-19 |
|----------|--------------------------------------------------------------------------------------------------|
| Lab parameters | During COVID-19 | After recovery from COVID-19 |
| Total bilirubin (mg/dL) | 1.04 | 0.78 |
| Direct bilirubin (mg/dL) | 0.37 | 0.18 |
| SGPT (U/L) | 126 | 23 |
| SGOT (U/L) | 61 | 25 |
| ALP (U/L) | 59 | 43 |
| S. total protein (g/dL) | 4.49 | 4.2 |
| S. albumin (g/dL) | 2.04 | 2.27 |
| S. globulin (g/dL) | 2.45 | 1.93 |
| A/G ratio | 0.83 | 1.18 |
| Monocytes (%) | 11.50 | 3.90 |
| Lymphocytes (%) | 19.70 | 12.30 |
| Neutrophils (%) | 65.20 | 81.30 |
| WBCs (cell/µL) | 2.8 x 10^9 | 5.7 x 10^9 |
| CRP (mg/L) | 11.50 | 5.01 |

A/G ratio, albumin to globulin ratio; ALP, alkaline phosphatase; CRP, C reactive protein; WBCs, white blood cells.

INVESTIGATIONS
Investigations have been mentioned as part of case presentation to maintain the continuity of case description, which authors felt essential.

TREATMENT
Treatment has been mentioned as part of case presentation to maintain the continuity of case description, which authors felt essential.

OUTCOME AND FOLLOW-UP
The patient was stable, recovered well and discharged on day 43. The patient completed 33 cycles (66 Gy) of external beam radiotherapy, with a post-therapy scan showing no residual or recurrent disease. The patient has completed 7 months of follow-up and has no surgery or COVID-19-related complication.

DISCUSSION
As per the literature search done on PubMed and Google Scholar with keywords “carcinoma larynx,” “laryngectomy,” “SARS-CoV-2,” and “COVID-19”, on 20 April 2021, this is the second case report of a successful recovery in a patient with laryngeal cancer developing SARS-CoV-2 infection in the postoperative period after TL. In the case series by Ricciardello et al, one case of SARS-CoV-2 infection following TL has been mentioned. Our case developed multiple complications, including PE, and is the first report in this regard.

The study by Wu et al reveals that 2%–11% of patients with COVID-19 had liver comorbidities, and 14%–53% of cases had abnormal alanine aminotransferase and aspartate aminotransferase levels during the progression of COVID-19 disease. In mild cases of COVID-19, there is liver damage and patients can return to normal without any special treatment. In the study by Mardani et al, white blood cell and lymphocyte counts were low, but the neutrophil count was higher in patients with positive RT-PCR for SARS-CoV-2 infection. Laboratory studies showed leukopenia with leucocyte counts of 2.91 x 10^9/L, 70.0% of neutrophil (NEU). Their result suggested that there may not be an effect on neutrophils by SARS-CoV-2 in the early course of the disease. It also suggests that SARS-CoV-2 might mainly affect lymphocytes, especially T lymphocytes. In our case, similar findings of raised levels of bilirubin, liver enzymes, neutrophil percentage and
cells in the upper respiratory tract and further invades the type 2 alveolar cells via ACE2 receptors.13 16 As age increases, ACE2 expression increases and increases the risk of COVID-19 manifestation.17 In our case, age being 67 years, increased the risk of adverse outcomes. Though the patient did not have preoperative comorbidities other than cancer; but at the time of being detected SARS-CoV-2 infection positive, the patient had already developed PE and neck infection, which again increased the risk of an adverse outcome.

There is an increased risk of lower respiratory tract infection in patients of TL.17 18 Permanent separation of the upper and lower airway resulting in loss of nasal physiological functions of filtration, humidification and temperature alteration of inhaled air leads to increased risk. Though there are no studies yet on SARS-CoV-2 infection in laryngectomised patients, authors hypothesise an increased risk of the infection due to altered physiology. The study by Paderno et al mentions two cases (one survival and one demise) that developed SARS-CoV-2 infection more than 5 years after undergoing TL.19 High-flow oxygen therapy in such patients increases the risk of airway crusting, which may require repeated tracheal toilet. In our case, high-flow oxygen therapy was required to keep oxygen saturation more than 90%; pre-emptive saline nebulisation and frequent tracheal toilet helped avoid tracheobronchial crusting. COVID-19 can lead to coagulopathy, which has a prothrombotic character with a high risk of venous thromboembolism.20 In our case, LMWH and eospirin were started for PE 12 days before being diagnosed as positive for SARS-CoV-2 infection; use of anticoagulants may be the reason behind mild COVID-19 in our case and the non-development of COVID-19-induced coagulopathy which could have worsened PE. LMWH has been reported to have beneficial effects (other than anticoagulant effect) in COVID-19, such as reducing inflammation, neutralisation of cytokines and chemokines, and partial attenuation of the cytokine storm. In the study by Shi et al, there were significant changes in interleukin 6 level, D-dimer and fibrinogen degradation products in the group of patients who received LMWH as compared with the group who did not receive it.21 22 In our case, though the patient developed multiple complications other than SARS-CoV-2 infection in the postoperative period, he could be managed successfully because of early recognition and timely intervention. The role of early intervention to reduce COVID-19-related complications has been emphasised in recent studies.23 24 No close contacts were infected from our case; the reason could be following stringent infection control policies and standard precautions. This case underlines the importance of research to better understand SARS-CoV-2 infection in patients with laryngeal cancer.

Acknowledgements We want to thank Dr Amit Kumar Tyagi (Assistant Professor, Department of Otorhinolaryngology, All India Institute of Medical Sciences, Rishikesh, India), Dr Pradip Pathak (Associate Professor, Department of Plastic Surgery, All India Institute of Medical Sciences, Rishikesh, India) and Dr Mayank Mishra (Associate Professor, Department of Pulmonary Medicine, All India Institute of Medical Sciences, Rishikesh, India) for their role and support in the clinical management of the patient.

Contributors AS and AB have contributed to manuscript writing, conception and idea for the manuscript. NR has contributed to data collection. MM has contributed to critical review and supervision of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

This article is made freely available for use in accordance with BMJ’s website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iD Abhishek Bhardwaj http://orcid.org/0000-0002-1217-9664

REFERENCES
1 World Health Organization. Coronavirus (COVID-19) events as they happen. Available: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen [Accessed 8 Apr 2020].
2 Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis 2020;36:101623. doi:10.1016/j.tmaid.2020.101623
3 Wolff D, Nee S, Hickey NS, et al. Risk factors for Covid-19 severity and fatality: a structured literature review. Infection 2021;49:15–28.
4 Marra A, Generali D, Zagami P, et al. Seroconversion in patients with cancer and oncology health care workers infected by SARS-CoV-2. Ann Oncol 2021;32:113–9.
5 van den Boer C, van Harten MC, Hilgers FJM, et al. Incidence of severe tracheobronchitis and pneumonia in laryngectomized patients: a retrospective clinical study and a European-wide survey among head and neck surgeons. Eur Arch Otorhinolaryngol 2014;271:3297–303.
6 Gosaín R, Abdou Y, Singh A, et al. COVID-19 and cancer: a comprehensive review. Curr Oncol Rep 2020;22:53.
7 Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21:335–7.
8 Ricciardiello F, Caraglia M, Romano GM, et al. Covid-19 laryngectomized patients care, on field experience, and considerations. Clin Case Rep 2021;10.1002/ccr3.3953. [Epub ahead of print: 21 Feb 2021].
9 Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. Jama Intern Med 2020;180:934–43.
10 Mardani R, Ahmadi Vasemehani A, Zali F, et al. Laboratory parameters in detection of COVID-19 patients with positive RT-PCR; a diagnostic accuracy study. Arch Acad Emerg Med 2020;8:e43.
11 Lei J, Li L, Li X, et al. Ct imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia. Radiology 2020;295:18.
12 Abate SM, Mantelaro E, Basiu B. Postoperative mortality among surgical patients with COVID-19: a systematic review and meta-analysis. Patient Saf Surg 2020;14:37.
13 Sanders JM, Monogue ML, Jodlowski TZ, et al. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. Jama 2020;323:1824–36.
14 Zhang L, Zhi F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020;31:894–901.
15 Parasher A. COVID-19: current understanding of its pathophysiology, clinical presentation and treatment. Postgrad Med J 2021;97:312–20.
16 Alpert N, Rapp JI, Marcellino B, et al. Clinical course of cancer patients with COVID-19: a retrospective cohort study. Jco Clin Cancer Spectr 2021;5:pkaa085.
17 Kelsey MF, Mitchell CA, Griffin M, et al. Prevalence of lower respiratory tract infections in hospitalized patients in the United Kingdom and Eire—the results from the Second National Prevalence Survey. J Hosp Infect 2000;46:12–22.
18 Haridl R, Andersson G, Frostell CG, et al. Respiratory tract colonization and infection in patients with chronic tracheostomy. A one-year study in patients living at home. Am J Respir Crit Care Med 1996;154:124–9.
19 Paderno A, Fior M, Berretti G, et al. COVID-19 and total Laryngectomy-A report of two cases. Ann Otol Rhinol Laryngol 2021;130:104–7.
20 Kollas A, Kirykoulis KG, Dimakakos E, et al. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol 2020;190:846–7.
21 Shi C, Wang C, Wang H, et al. The potential of low molecular weight heparin to mitigate cytokine storm in severe COVID-19 patients: a retrospective cohort study. Clin Transl Sci 2020;13:1087–95.
22 Buyssers B, Yanginlar C, Maciej-Hulme ML, et al. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. EBioMedicine 2020;59:102969.
23 Goyal DK, Mansab F, Iqbal A, et al. Early intervention likely improves mortality in COVID-19 infection. Clin Med 2020;20:248–50.
24 Sun Q, Qiu H, Huang M, et al. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. Ann Intensive Care 2020;10:33.
