



Case report

Tocilizumab in SARS-COVID19 following postoperative laparoscopic transhiatal esophagectomy for the adenocarcinoma of esophagogastric tumor: A case report

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ABSTRACT

Introduction and importance: Esophagectomy for esophageal cancer is one of the most challenging surgical procedures, with high rates of morbidity, especially from respiratory complications. SARS-COVID19 represents a health threat nowadays. Peri-operative SARS-COVID19 infection after esophagectomy might negatively affect the postoperative outcomes. The use of tocilizumab as an alternative to reduce the inflammatory response in SARS-COVID19 is an option that has not been described in the literature after esophagectomy.

Case presentation: A SARS-COVID19-vaccinated (CORONAVAC) 73-year-old man with pulmonary emphysema, coronary artery disease, previous asymptomatic pulmonary embolism, and adenocarcinoma of the esophagogastric junction tumor was submitted to laparoscopic transhiatal esophagectomy (ypT2N0M0) after perioperative neoadjuvant chemotherapy. He was also infected with SARS-COVID19, confirmed by PCR test at the 14th postoperative day. During follow-up, mild hypoxemia persisted without evidence of infection except for SARS-COVID19, and a high-flow cannula was required to maintain oxygenation. Tocilizumab was administered following high parameters of a high-flow cannula, and invasive mechanical ventilation was avoided.

Discussion: Besides of the risk of secondary infection, after administration of tocilizumab, the parameters of oxygen supplementation were systematically reduced, and he stayed in the ICU for seven days. He was discharged from the ward six days later. He developed late cervical anastomotic leakage, which was treated with conservative therapy.

Conclusion: Although the patient had high-risk comorbidities, esophagectomy, and SARS-COVID19 infection, the use of tocilizumab was safe and improved the pulmonary recovery.

1. Introduction

After the beginning of pandemic COVID-19, the time of oncological surgery treatment has become a critical, debatable issue because of excessive postoperative pulmonary complications [1]. In addition to this, the onset of COVID-19 pandemic has also caused relevant mortality rates in patients with perioperative SARS-COVID19 infection [2]. Esophagectomy for esophageal cancer is one of the most complex surgeries with significant respiratory complications, such as atelectasis and pneumonia. In a similar way, perioperative SARS-COVID19 after

esophagectomy might be more challenging to treat because the positive pressure of oxygen might interfere adversely with the healing of cervical anastomosis, and differentiating pulmonary injuries (inflammatory or infection) might be challenging.

Tocilizumab is a recombinant anti-interleukin-6 monoclonal antibody that was employed to decrease the mortality and progression to invasive mechanical ventilation in patients with severe SARS-COVID19 pulmonary symptoms [3]. However, one of the feared side effects is the exacerbation of infection and sepsis, which is a critical issue to not use tocilizumab after complex surgeries with a substantial risk of infection.

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Therefore, the use of tocilizumab for the respiratory manifestation of SARS-COVID19 after esophagectomy is a challenging decision considering the risk of immunodepression. The following report was done in line with the SCARE criteria [4].

2. Case report

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. We report a 73-year-old man was diagnosed with adenocarcinoma of the esophagogastric junction and underwent perioperative treatment with docetaxel-based triplet FLOT (fluorouracil plus leucovorin, oxaliplatin, and docetaxel) for five cycles. The patient was vaccinated with two doses of CORONAVAC for SARS-COVID19 (one-month interval), and surgery was performed three months after the last dose. Because of emphysema (an obstructive pulmonary disease), previous angioplasty with mild coronary compromised function, and a recent diagnosis of asymptomatic segmental pulmonary thromboembolism, laparoscopic transhiatal esophagectomy with posterior mediastinal gastric pull-up and supercharged cervical anastomosis (microanastomosis from the cervical transverse artery and external jugular vein to short vessels from the greater curvature of the stomach) was selected to minimize the risk of pulmonary and clinical complications.

The patient underwent laparoscopic transhiatal esophagectomy three weeks into the fifth FLOT cycle with an experienced oncological surgeon. The patient remained in the intensive care unit (ICU) during the first five postoperative days (PODs) only with a residual right pneumothorax, which was re-drained, and he was transferred to the ward on POD 5. The patient was stable with no complaints, on POD 8 no evidence of anastomotic leakage was seen in contrast dynamic esophagogram. Full anticoagulation for the pulmonary thromboembolism and oral intake of food was started on the same day. On POD 10, the patient had a massive bleeding from the left cervicotomy, which required surgical re-intervention with cervical exploration, bleeding control and he was transferred to intensive care unit. Anticoagulation was interrupted, and enteral feeding was continued. The patient improved overall on

PODs 11–13. However, on POD 14, he developed severe hypoxemia but vasopressors were not necessary. At this time, the antibiotics were switched from cefalexin to meropenem and teicoplanin. Nasopharyngeal swabs were collected for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcription-polymerase chain reaction (RT-PCR), and positive results were obtained the following day. On POD 16, the patient again developed progressive hypoxemia, requiring a high-flow cannula. (Fig. 1).

On POD 18, the C-reactive protein, a serum inflammatory marker, increased, but procalcitonin level was normal. Only clinical assessment of respiratory dysfunction without any cardiovascular collapse was made, even with a high-flow cannula. At this time, we assumed that hypoxemia was related to SARS-COVID19, so we considered administering tocilizumab (4 mg/kg) single dose. The interleukin-6 level was measured; results showed an increased level at 116 pg/ml (reference: 1.5–7.0 pg/ml).

Oxygen saturation improved substantially by POD 21 after the administration of tocilizumab, and the flowmetry and fraction of inspired oxygen (FiO₂) of the high-flow cannula decreased systematically. On POD 26, the oxygen supplement was changed to a nasal catheter. Two days later, he was transferred to the ward, where he remained for another six days.

After POD 21, clinical suspicion of anastomotic leakage was confirmed after pus and saliva were observed on the drain component. A 75 mmHg vacuum negative pressure was performed to form a guided self-drainage to the cervicotomy. This vacuum system was maintained until POD 32. Subsequently, the leakage component underwent spontaneous drainage from the cervicotomy incision. The enteral feeding tube was removed on POD 30, and oral pasty feeding was allowed. The patient was discharged on POD 34. The final pathological stage was ypT2N0M0 (42 Lymphnodes retrieved, no metastatic lymphnode was found), and according to our results, the overall survival is 56% and the disease-free survival 55.3%. (Fig. 2).

3. Discussion

Oncological patients had their surgical treatments delayed since the emergence of the SARS-COVID19 pandemic, mainly due to the risk of

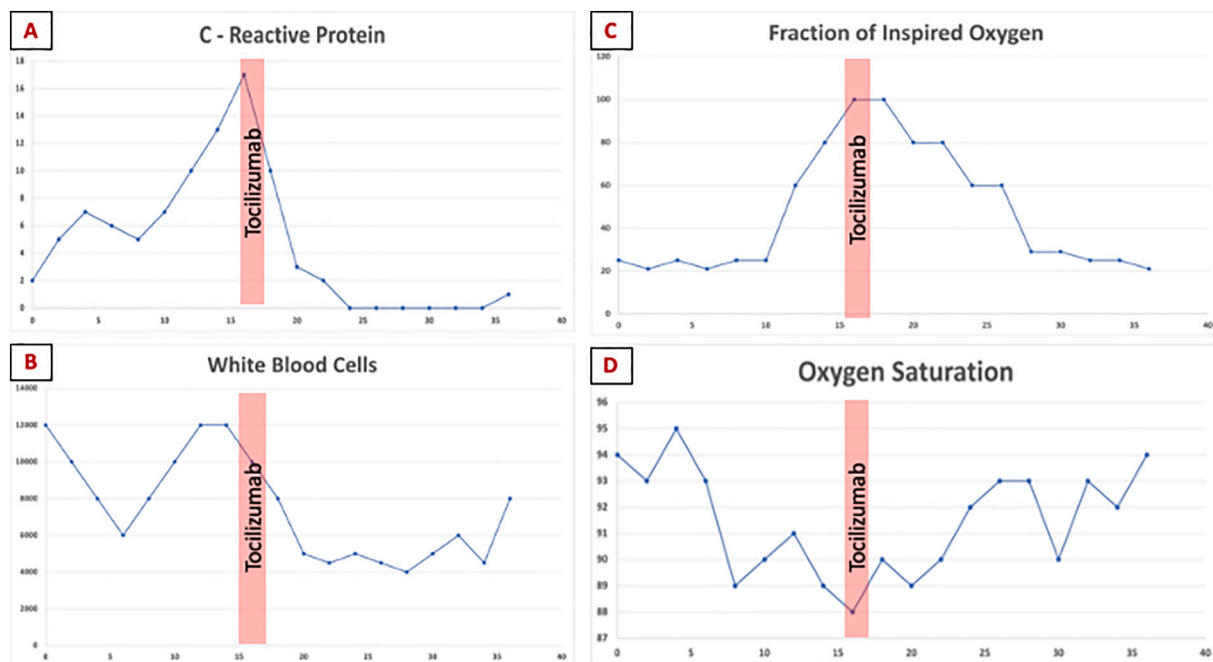


Fig. 1. Graphics of laboratory and oxygenation controls. A: Dosage of C reactive protein according to post-operative day; B: Dosage of C white blood cell according to post-operative day; C: Levels of fraction of inspired oxygen according to post-operative day; D: Levels of oxygen saturation according to post-operative day.

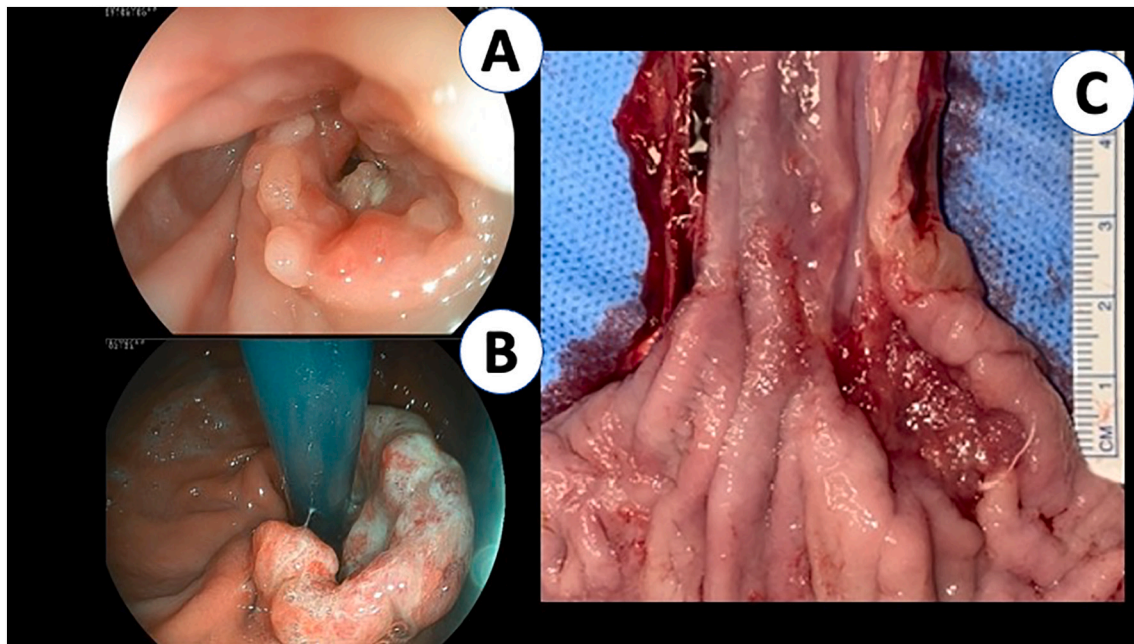


Fig. 2. Photos of the adenocarcinoma of the esophagogastric junction. A: Upper endoscopy photo, ulcerated lesion in distal esophagus; B: Upper endoscopy photo, ulcerated lesion in the cardia; C: Post-operative image, pathologic specimen of the esophagogastric junction.

considerable morbidity rates, respiratory illness with hypoxemia, and prolonged ventilatory support. Because of this, different COVID-19 free surgical pathways attempted to provide safe elective cancer surgery [11], as the vaccination program take years to be delivered, particularly in low and middle-income countries [5], such as Brazil thus, patients may be infected with SARS-COVID19.

Unfortunately, no drugs are available to neutralize SARS-COVID19 infection. However, tocilizumab has been used as an immunomodulatory drug to control the cytokine storm caused by COVID19. Tocilizumab mainly inhibits interleukin-6, as observed in B-cell chronic lymphocytic leukemia treatment [5]. Two main factors affect the outcome of tocilizumab use: severe illness without invasive mechanical ventilation and severity of cytokine storm measured mainly by C-reactive protein and interleukin-6 levels; both are common and are related to prognosis [7,8].

Esophagectomy for esophageal cancer is a well-known procedure associated with considerable morbidity. Minimally invasive surgery improved results, especially with transhiatal esophagectomy, this resulted to fewer days in the ICU and shorter hospital stay [9]. We have systematically performed a vascular microvessel anastomosis (supercharged procedure) in patients with high-risk postoperative complications since we are used to perform cervical esophagogastric anastomosis. This procedure could improve the perfusion of esophagogastric anastomosis and reduce leakage [10].

The patient had a considerable number of comorbidities and compromised pulmonary function (emphysema and previous asymptomatic pulmonary embolism). These were the reasons why we selected the laparoscopic transhiatal approach. In terms of postoperative outcomes, all endeavors focused on the care of pulmonary function and reducing the risk of anastomotic leakage. Positive pressure is a well-known factor that could interfere with anastomotic healing, and it was contraindicated in postoperative recovery. However, due to hypoxemia after POD 14, the oxygen supplementation was changed from catheter to high-flow cannula. After the contrast X-ray swallowing test, we assumed that there was minimal chance of anastomotic leakage. After the usual dosage of pro-calcitonin (inferior to 2 mg/dl), we concluded that tocilizumab can be introduced. The main risk of its administration is the side effect of immunodepression in a recent postoperative oncological surgery with a considerable rate of complications and infection [11].

Potentially, this situation could lead to further complications, facilitating a secondary infection (bacterial or fungal) or multiple organ dysfunction [7,8].

The recommendations for the appropriate dosage of tocilizumab was 4 mg/kg to 8 mg/kg. Some studies have recommended splitting into two doses. Due to the patient's frailty, postoperative conditions, and clinical assessment, we opted for a dosage of 4 mg/kg. Another factor related to dosage decision was the previous vaccination with CORONAVAC. Among people who were fully immunized, the adjusted vaccine effectiveness was 65.9% and to prevent COVID-19-related death was 86.3% [5].

After this point, the levels of C-reactive protein and white blood cells were systematically reduced. Clinical conditions associated with the expected values of pro-calcitonin guided us to ensure no infections in clinical outcomes. The patient clinically improved after rehabilitation and progression of food consistency, and after the anastomotic leakage resolved.

The only side effect that might be related to tocilizumab was the late occurrence of anastomotic leakage. However, high-flow pressure cannula of oxygen (positive pressure), use of corticoids, inflammatory status, and constant coughing might also contribute to cervical fistula. However, the patient had no site infection or abscess, since the contents of the fistula had been drained naturally to the left cervical incision.

Few studies have described the use of tocilizumab after the post-operative period [6,7,8], and to the best of our knowledge, this is the first case described in the literature to be associated with major surgical procedures and successful outcomes.

4. Conclusion

Although the patient had high-risk comorbidities, esophagectomy, and SARS-COVID19 infection, the use of tocilizumab was safe and improved pulmonary recovery.

Declaration of competing interest

None to declare.

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Ethical approval and consent

Ethical and consent approval exemption were given for this study.

Research registration

Not applicable.

Guarantor

F.R.T.

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