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SURGERY FOR OBESITY AND RELATED DISEASES

Video case report

Colorectal surgery obesity-related morbidity during COVID-19

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Abstract Tocilizumab, a monoclonal antiinterluekin-6 receptor antibody, has been empirically used in the treatment of cytokine release syndrome associated with severe coronavirus disease 2019 infections. The efficacy and safety of these medications for these patients is unknown. The purpose of this report was to present a case of acute large bowel perforation in a morbidly obese patient with coronavirus disease 2019 pneumonia who received empiric Tocilizumab. This case report analyzes the risks of acute large bowel perforation after using this medication empirically and discusses the appropriate management of this adverse event. (Surg Obes Relat Dis 2020;16:1372–1375.) © 2020 American Society for Bariatric Surgery. Published by Elsevier Inc. All rights reserved.

Key words: COVID-19; SARS-CoV-2 coronavirus; Tocilizumab; IL-6; Corticosteroids; Bowel perforation; Colonic perforation

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus disease 2019 (COVID-19) crisis is considered the pandemic of the century [1]. The disease has rapidly spread around the world and has been acknowledged as an international public health emergency because of a lack of sufficient resources to care for the increasing number of patients with acute respiratory distress syndrome due to COVID-19 [2]. Infected patients may present as asymptomatic carriers or may develop symptoms ranging from mild upper respiratory symptoms to signs and symptoms of multiorgan failure [3]. The SARS-CoV-2 coronavirus produces a profound inflammatory state in the human body with marked elevation of serum cytokines, especially interferon gamma, tumor necrosis factor alpha, interleukin (IL)-17, IL-8, and IL-6, which can lead to respiratory failure requiring mechanical ventilation, disseminated intravascular coagulation, and multiorgan failure [4]. Thus far, no curative therapy or protective vaccines are available. Empiric pharmacologic treatments have been used with mixed results, including Hydroxychloroquine, Remdesivir, and Tocilizumab [5–7]. These medications are associated with deleterious adverse effects but because of the lack of viable treatments, physicians have used them around the world in an attempt to improve survival in critically ill patients with COVID-19. The efficacy and safety of these medications for these patients is unknown.

The purpose of this case report was to analyze the risks of acute large bowel perforation after using Tocilizumab empirically for COVID-19 pneumonia in morbidly obese patients and discuss the appropriate management of this adverse event.

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Case report

We present the case of a 54-year-old obese female with a past medical history of hypertension who was brought by Emergency Medical Service to the hospital because of progressive decline in mental status in the context of high-grade fever, dyspnea, orthopnea, nonproductive cough, and fatigue over the previous 5 days. Upon arrival to the hospital, the patient was febrile up to 103.3°F, tachycardic, tachypneic, with oxygen saturation of 92% on a nonrebreather mask. Rapid COVID-19 testing using polymerase chain reaction returned positive. Other laboratory workup was significant for C-reactive protein of 22.8 mg/L and N-terminal prohormone of brain natriuretic peptide (NT-Pro BNP) of 567 pg/mL. Chest X-ray showed multifocal airspace infiltrates suspicious for multifocal pneumonia with small pleural effusions (Fig. 1). Arterial blood gas showed pH of 7.49, carbon dioxide level of 38 mm Hg, and arterial oxygen of 69 mm Hg. Due to progressive respiratory insufficiency, the patient was intubated and was empirically treated with Levofloxacin 500 mg and Ceftriaxone 1 g for presumed superimposed pneumonia. Additionally, she also received Hydroxychloroquine 200 mg twice daily for 5 days. Because of persistent hypoxemic respiratory failure, she was treated for 4 days with pronation, paralysis, and inhaled epoprostenol. However, the patient did not show signs of improvement. She was subsequently started on veno-venous extracorporeal membrane oxygenation (ECMO) treatment for 21 days. During this time, the antibiotic spectrum was broadened to cover for hospital-associated pneumonia and she additionally received empiric Tocilizumab 400 mg intravenously. As a result of the persistent need for ventilatory support, the patient underwent tracheostomy and was subsequently decannulated from veno-venous ECMO after showing steady improvement in her respiratory status. Before decannulation, the patient had episodes of epistaxis related to ECMO anticoagulation, which required nasal packing. Because of concerns of localized swelling of the tongue and pharyngeal edema, she also received intravenous 2-mg Dexamethasone. One day after decannulation, the patient had bright red bleeding per rectum and developed tachycardia and hypotension requiring vasopressor support. Chest X-ray showed free air under the right hemidiaphragm (Fig. 2), thereby raising concern for presumed bowel perforation. Despite being high risk, in view of her age and recent recovery from ECMO, the decision was made to take her to the operating room after discussion with a multidisciplinary team and the family members. Intraoperatively, 2 L of fecal material was found in the intraperitoneal cavity. The abdominal cavity was washed with 10 L of fluids, including all 4 quadrants. The cecum was found to be ischemic and perforated. The stomach and duodenum appeared healthy. The small bowel was run from the jejunum to the terminal ileum with no signs of ischemia. Because of her tenuous status and significant intraabdominal sepsis, she underwent right hemicolectomy with end ileostomy and Hartmann closure of the colon. Histopathologically, the tissue demonstrated transmural coagulative necrosis involving the cecum and extensive fibrinopurulent serositis (Fig. 3). There was no malignancy in the specimen. Postoperatively, the patient received antibiotics and vasopressors for septic shock. The patient demonstrated progressive improvement in her respiratory status and hemodynamics, was weaned off vasopressors, and discharged to a long-term acute care facility.

Discussion

COVID-19 has rapidly spread around the world. Over the last few months, there have been numerous publications in the literature that describe the devastating clinical effects

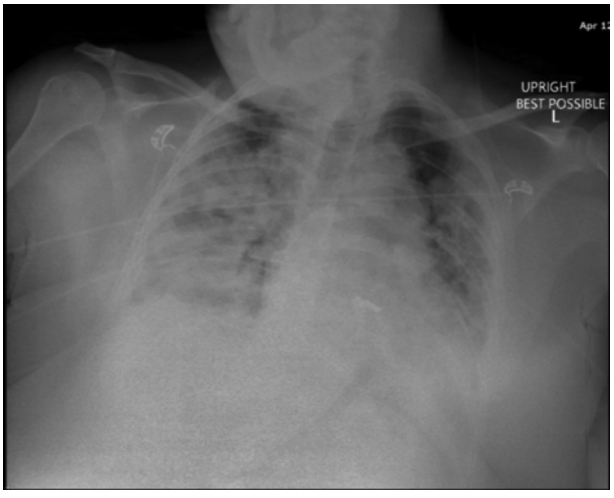

Fig. 1. Chest X-ray with multispace air opacities.

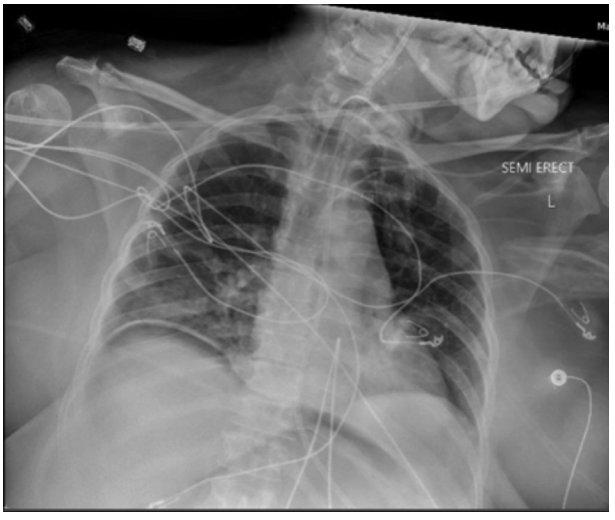

Fig. 2. Chest X-ray demonstrating pneumoperitoneum.

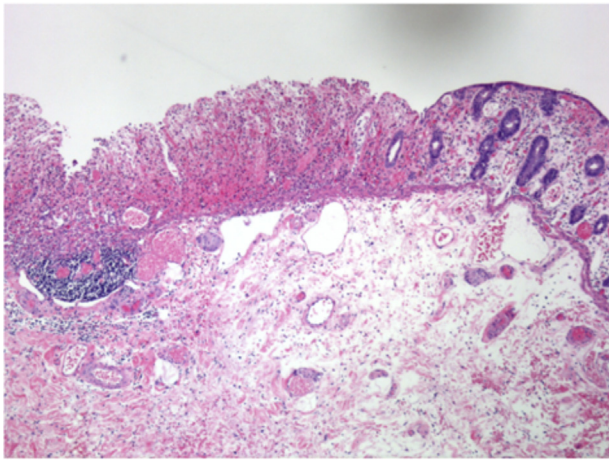

Fig. 3. Transmural coagulative necrosis involving the cecum and extensive fibrinopurulent serositis.

of this virus [8–11]. However, to the best of our knowledge, this is the first report describing bowel perforation in a critically ill COVID-19–positive patient receiving empiric Tocilizumab. New therapeutic approaches are being developed to treat critically ill COVID-19–positive patients and rely on controlling the proinflammatory cytokines, mainly IL-6, IL-10, and tumor necrosis factor-α. Tocilizumab, a monoclonal antiIL-6 receptor antibody primarily used for rheumatologic conditions, has been used in the management of cytokine release syndrome associated with severe COVID-19 infection [12]. A randomized, double-blind, placebo-controlled phase III clinical trial is currently underway to evaluate the safety and efficacy of tocilizumab plus standard of care in hospitalized patients with severe SARS-CoV-2 coronavirus pneumonia compared with placebo plus standard of care. The primary and secondary endpoints of the study include clinical status, mortality, mechanical ventilation, and intensive care unit variables [13]. Although promising in controlling the disease in certain patients with hyperinflammatory phenotype, its safety and efficacy are still under debate.

One of the most commonly reported complications of Tocilizumab in patients with rheumatologic conditions is the increased risk of lower gastrointestinal perforations. Strangfeld et al. [14] reported a significant increased risk of bowel perforations in patients using Tocilizumab (2.7 events per 1000 person-years) when they compared them with patients taking other biological agents. The 30-day mortality rate among patients with bowel perforation was 46%. The pathophysiology is not completely understood; however, prior diverticulitis is a risk factor for the development of bowel perforation in patients taking Tocilizumab. Interestingly, our patient did not have diverticulosis seen on abdominal imaging. In another retrospective study, it was shown that the concomitant use of Tocilizumab and Prednisone causes a higher incidence of lower gastrointestinal perforations in comparison to other tumor necrosis alpha inhibitors [15]. Our patient received both medications before the acute large bowel perforation occurred, because she received empiric Tocilizumab for COVID-19 pneumonia and Dexamethasone for several days for pharyngeal edema.

It has been established that COVID-19 infects the human organism by binding the angiotensin-converting enzyme receptors, similar to the mechanism previously described with the SARS pathogen [16]. Angiotensin-converting enzyme receptors are not only highly expressed in the airway and lung tissue but also present in the gastrointestinal tract. Viral nucleic acids have been found in the stool and saliva of COVID-19–positive patients [17]. These findings support the possibility that this virus could spread through fecal oral transmission. A recent study showed that in patients who manifested with gastrointestinal complaints, the virus was isolated from fecal material in early stages of the infection [18]. More research is needed to determine if the immune response to the virus could be a cause of gastrointestinal perforations.

Another emerging theory for many of the complications noted in critically ill COVID-19 patients is the hypercoagulable state caused by the virus. The measurement of D-dimer levels has proven to be useful in predicting the risk of thrombosis and mortality in this patient population, as recently suggested by a study conducted in Wuhan [19]. An observational study that included 184 COVID-19–positive cases showed a 31% incidence of thrombotic events. Anticoagulation in these patients helped prevent the thrombotic effects of this virus. None of the patients observed in this study were diagnosed with disseminated intravascular coagulation. Pulmonary embolism was the most frequent thrombotic complication (n = 25, 81%) [20]. There is growing evidence that many of the complications and deaths are related to thrombotic events in critically ill COVID-19–positive patients. Most physicians are now using prophylactic anticoagulation medications to treat patients infected with COVID-19 [21,22]. Currently, there are no reports of bowel ischemia or perforation caused by thrombotic events; however, this may be a contributing factor for acute large bowel perforation in COVID-19–positive patients treated empirically with Tocilizumab.

Additionally, hemodynamically unstable critically ill COVID-19–positive patients may require vasoactive medication, potentially leading to intestinal hypoperfusion and intestinal ischemia. The pathogenesis is believed to be an interrelationship of several factors, such as inflammatory cells, activation of proinflammatory cytokine cascade, interruption of microcirculatory blood flow, as well as the functional integrity of the intestinal mucosa [23]. Intestinal hypoperfusion may have been a contributing factor; however, it is unlikely to be the main etiology of large bowel perforation in the case described herein, because there was no

evidence of ischemia in other areas of the small or large intestine supplied by the superior mesenteric artery.

Conclusion

This case report describes a rare case of colonic perforation in a critically ill, morbidly obese patient with COVID-19 pneumonia on empiric Tocilizumab therapy. This report adds data to the currently small body of literature for this finding. It emphasizes the importance of close monitoring for gastrointestinal events in patients infected with COVID-19 receiving Tocilizumab empirically. Further studies are needed to better understand the safety and efficacy of tocilizumab plus standard of care in hospitalized patients with severe COVID-19 infection.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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