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Tocilizumab-induced acute worsening of a pyogenic liver abscess in a patient with severe COVID-19

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Abstract

Several therapeutic agents have been evaluated for the treatment of severe coronavirus disease 2019 (COVID-19). Tocilizumab (an interleukin-6 receptor antagonist) is an approved drug to treat cytokine storms caused by severe COVID-19. However, several case reports suggested that tocilizumab worsens pyogenic infections. The increasing use of tocilizumab requires consideration of a higher index of clinical suspicion for rare side effects.

We report a case of severe COVID-19 with a cytokine storm in a patient who had been treated with tocilizumab. A large liver abscess was detected two days after the initial dose, this was not revealed in a chest computed tomography scan obtained two weeks earlier. Bacterial culture of blood and drainage from the hepatic abscess yielded a growth of *Klebsiella pneumoniae* which was treated with amoxycillin-clavulanic acid. We propose that the use of tocilizumab exacerbated a bacterial infection and increased the severity of a liver abscess.

Keywords

SARS-CoV-2; COVID-19; Liver abscess; Tocilizumab; Cytokine storm.

Introduction

SARS-CoV-2 infection was first reported from Wuhan, China, in December 2019, and was officially called coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) in February 2019. As of December 2021, the WHO reported approximately 270,791,973 confirmed cases of COVID-19; approximately 5,318,216 deaths; and 8,200,642,671 vaccine doses administered worldwide.

The pathophysiology of COVID-19 involves the binding of the virus to the alveolar epithelium, which

leads to the activation of the adaptive and innate immune systems, resulting in an inflammatory cascade and the release of interleukin-6 (IL-6) [1].

Increased levels of IL-6 are associated with serious and sometimes fatal outcomes in COVID-19. Tocilizumab is a humanized recombinant monoclonal antibody that acts as an IL-6 receptor antagonist by binding to soluble or membrane-type IL-6 receptors [2].

Given the absence of specific antiviral treatment against COVID-19 and that IL-6 plays a role in the COVID-19-induced cytokine storm-cytokine release syndrome, the use of tocilizumab is frequently considered for the treatment of patients with COVID-19. IL-6 amplifies the cytokine reaction, which is eventually followed by an infiltration of inflammatory monocytes, macrophages, and lymphocytes into the lungs. In addition, IL-6 was found to be associated with a decrease in human leukocyte antigen-DR isotype expression, leading to lymphoid function defects [2]. Although tocilizumab effectively inhibits IL-6 expression, an impaired immune response may predispose patients to secondary bacterial infections as reported here.

Case Report

A 54-year-old man who smoked and had type 2 diabetes mellitus and hypertension, was diagnosed with mild COVID-19 and a CT chest didn't show any signs of consolidations or lung infiltrates. Due to the mild disease, he self-isolated at home with symptomatic therapy. 10 days later, he visited the secondary care hospital in Makkah, Saudi Arabia complaining of shortness of breath and dry cough. On presentation, the patient was febrile, had stable vitals, and maintained an oxygen saturation in room air.

After 24 h, he became hypoxemic requiring 5 L of oxygen. He was started on oral favipiravir and intravenous dexamethasone. Despite this therapy, he started to deteriorate with increasing oxygen requirements and significantly elevated inflammatory markers. Therefore, he was given an initial dose of tocilizumab 800 mg IV.

Two days following tocilizumab therapy, the patient complained of right upper quadrant abdominal pain associated with fever and jaundice. Liver profile showed a significant increase in enzymes.

Abdominal Computed Tomography (CT) showed an enlarged liver and a large fluid density lesion with an irregular outline in the right lobe, with multiple variable-sized air loculi inside (air fluid level). In addition, there was rim enhancement (inner rim) and a thin outer rim of hypo-attenuation (double target sign), which measured 15 × 14 × 18 cm, suggestive of a huge abscess with an air fluid level. No intrahepatic or extrahepatic biliary radicle dilatation was seen (Figure 1). Under CT guidance the hepatic abscess drain was inserted and around 300ml of purulent fluid was drained in initial 24 hours. He was referred to our hospital, a tertiary care center for further management. Blood and drain cultures showed the growth of *Klebsiella pneumoniae.* The patient was treated intravenously with piperacillin-tazobactam for initial 24 days with dramatic clinical improvement. The patient was discharged on oral amoxycillin-clavulanic acid, based on bacterial susceptibility. At follow up, two weeks later in the out-patients he was found to be clinically well with normalization of liver profile apart from raised ALP. A follow up CT done at 6 weeks

from date of discharge showed, significant interval decreases in size of the intrahepatic abscess collection; the residual collection measured 2.6 x 2 x 1.6 cm with internal pocket of gas, which was previously 8.6 x 10.6 x 11.4 cm in AP, transverse and CC dimensions (Figure 3).

Figure 1: Abdominal computed tomography performed four days after admission, showed an enlarged liver and a large fluid density lesion.

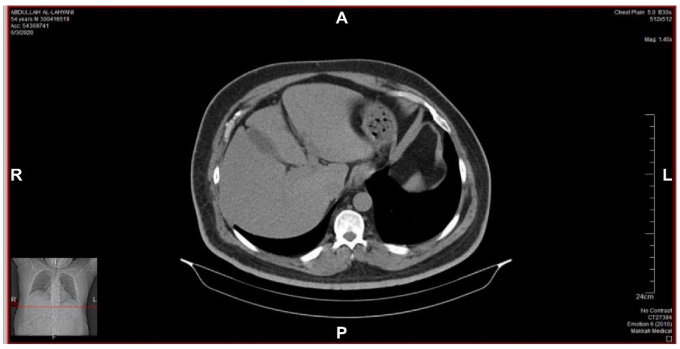

Figure 2: Liver cuts from the chest computed tomography performed two weeks prior to admission does not show any signs of a liver abscess.

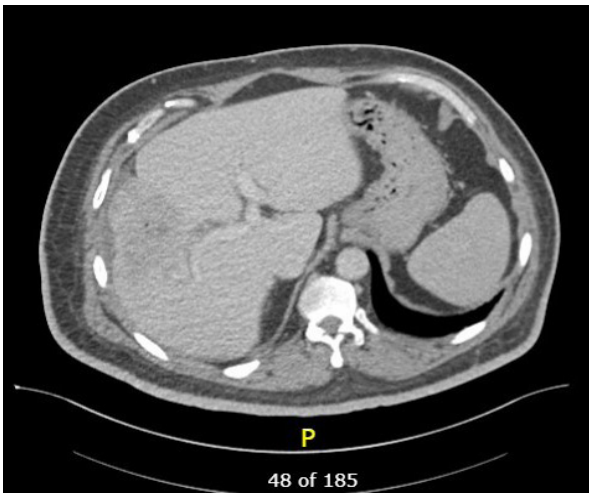

Figure 3: A follow up CT done at 6weeks from date of discharge, showed significant interval decrease in size of the intrahepatic abscess collection.

Discussion

COVID-19 has been a devastating pandemic caused by SARS-CoV-2 that primarily infects the chest. Once an unknown infection, considerable knowledge over the last three years has to the recognition that the deadly virus does infect other organs including the digestive system. Liver injury is now understood to be common in COVID 19, but fortuitously mild. Most often manifesting in form of abnormal liver test prevalent in around 14-53% of cases and are more frequently seen in severe infection than in mild [3]. The pattern of abnormality is mainly hepatocellular with AST, ALT, gamma-glutamyl transferase, bilirubin, and alkaline phosphatase raising in 23.2%, 21.2%, 15%, 9.7% and 4% of cases respectively [4]. The liver

enzyme abnormality declines to baseline in most patients over time, however when high it predicts poor prognosis including intensive care admissions, mechanical ventilation and mortality [5]. Multiple potential factors contribute to the pathophysiology of liver injury and include direct SARS-CoV-2 liver damage to indirect causes like systemic immune response, hypoxia, reperfusion/congestion, and drug-induced injury [5]. Although clinically significant liver damage is rare cases of liver abscess development on background of liver necrosis and portal vein thrombosis have been reported [6,7].

Tocilizumab (TZB) is a humanized monoclonal antibody that binds to interleukin 6 receptor, inhibiting its multiple pro-inflammatory activities. Following FDA approval, TZB has been recommended for use in hospitalized COVID-19 patients who progress despite dexamethasone therapy requiring high flow oxygen with rapidly rising inflammatory markers [8,9]. Due to the short period since approval, TZB safety profile is still under review in the context of use in COVID 19 patients. Most of the safety data on TZB comes from studies in chronic inflammatory conditions like rheumatoid arthritis. The most common reported adverse events included bacterial infections like upper respiratory tract infections, skin lesions and gastrointestinal side effects. In addition, abnormality of laboratory results in form of rising liver enzymes, abnormal lipid profile and low neutrophil and platelet counts have been documented [10]. The cause of TZB induced liver toxicity is not fully clear; however, the likely proposed mechanism could be IL-6 blockade, as it helps in promoting hepatocyte regeneration and protects against injury due to ischemia, reperfusion and toxins [11]. Rise in serum Aminotransferase (ALT) is the salient liver toxicity seen in up to 50% of patients with levels rising to 5 times the normal. Fortunately, the liver damage is mild with spontaneous resolution in weeks [12]. Rarely, it causes severe liver injury with few reports of hepatic necrosis, acute and fulminant hepatitis mainly in patients on concomitant hepatotoxic medications [13]. Literature on TZB induced hepatic injury when used in COVID – 19 is limited. The prevalence of reported hepatic injury in clinical trials was around 3% and 15% in case series [14,15]. The hepatic injury mainly is mild rise in ALT that resolves within weeks; nevertheless, a single case report documented a 40-fold increase without significant clinical damage [16]. However, TZB is one of the drugs that is strongly associated with drug induced liver injury in COVID-19 hospitalized patients [17]. No case of significant hepatic injury or of liver abscess has been reported in patients receiving TZB for COVID-19 treatment.

When we retrospectively reviewed the liver cuts from the chest CT of our patient done two weeks prior to admission, to our surprise, we did not observe any signs of liver abscess (Figure 2). It is unlikely that a liver abscess had formed and reached such a large size within two days of tocilizumab treatment. In our case, it is probable that the tocilizumab dose led to acute worsening of a pre-existing small liver abscess that may have formed within the two weeks following the last imaging. Another possibility could be that our patient initially had the pathophysiology of post COVID-19 necrosis and liver abscess, as seen in the case of Liemarto et al. [7], followed by secondary pyogenic infection, which was further worsened with tocilizumab.

Conclusion

In conclusion, the use of tocilizumab has increased significantly since the beginning of the COVID-19 pandemic. This has led to an increase in the incidence of uncommon adverse effects, including worsening of pyogenic infections, such as abscesses. Our case emphasizes the need to have a high index of suspicion and a low threshold for imaging in patients treated with tocilizumab if they develop signs or symptoms suggestive of infection. It also stresses the need for systematic studies to evaluate the incidence of such adverse effects and define vulnerable populations so that appropriate screening methods can be adopted for early diagnosis and treatment. This will ultimately help in reducing morbidity and mortality.

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