Case Report

ISSN: 1735-0344 *Tanaffos 2023; 22(1): 167-171*

TANAFFOS

Cytokine Release Syndrome (CRS) in Severe COVID-19 Patients: Two Controversial and Interesting Case Reports and Literature Review

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Received: 23 January 2022
Accepted: 9 November 2022

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Background: Cytokine release syndrome (CRS) represents a potentially life-threatening and systematic inflammatory response where it is noted an increase of secretion of proinflammatory cytokines from lymphocytes, myeloid cells like macrophages, dendritic cells, and monocytes. This syndrome is characteristic of some conditions such as viral infections, administration of antibody-based therapy, auto-immune disease, and immunotherapy, especially in severe COVID-19 patients.

Case reports: We presented two cases of COVID-19 patients in which the clinical picture significantly deteriorated during hospitalization, where the value of CRP, ferritin, LDH, and IL-6 dramatically increased, especially values of IL-6 were recorded over 2000. We treated them with third-generation cephalosporins, carbapenems, glycopeptides, metronidazole, anti-IL-6 inhibitor, low molecular weight heparin (LMWH), glucocorticoids, immunoglobulins (IVIG), and vitamins. Both patients were successfully treated and were discharged from the hospital with a recommendation for oral anticoagulant therapy.

Conclusion: CRS is a complex syndrome. In the future, it is necessary to educate doctors about this syndrome, as well as to develop drugs whose goal would be to reduce the inflammatory response in already developed diseases.

Keywords: COVID-19; Cytokine release syndrome; Inflammation; IL-6

INTRODUCTION

Cytokine release syndrome (CRS) represents a potentially life-threatening and systematic inflammatory response that has been observed to occur after antibody administration and adoptive T cell therapy. The term CRS in clinical practice appeared during the 1990s when the anti-T-cell antibody muromonab CD3 (OKT3) was presented as an immunosuppressive treatment for solid organ transplantation. According to the literature, in a healthy organism, there is a balance between anti and pro-inflammatory cytokines but in some conditions like a viral infection, administration of antibody-based therapy, auto-immune disease, and immunotherapy could dramatically increase secretion of proinflammatory cytokines from lymphocytes (B cells, T cells, and natural killer cells) and myeloid cells like macrophages, dendritic cells, and monocytes (1, 2). CRS may start under the picture of mild symptoms such as fatigue, fever, myalgia, and progress to the severe clinical picture of hypotension, renal and/or liver toxicity, acute respiratory distress syndrome (ARDS), and disseminated intravascular coagulation (DIC) (1). This problem is especially important in COVID-19 infection. Critically ill COVID-19 patients with pneumonia are at the highest risk of developing CRS (3). In this topic, we

presented two cases who were treated in a hospital and developed CRS.

For literature review, we selected substantial studies from databases of PubMed, Embase, and Cochrane Library. The following Mesh terms were used: "cytokine release syndrome", "COVID-19", "SARS-CoV2 infection", "IL-6", and "pro-inflammatory cytokines". Headlines, abstracts, and full-text articles of possibly useful studies were independently checked by two researchers. We analyzed papers published only in the English language. The reference lists of articles were scrutinized for detecting studies that were not grabbed by the electronic search. The study was conducted using literature published from January 2014 to January 2021. With a detailed analysis of the literature, we included 12 articles based on the above-mentioned keywords. The study was approved by the local ethical committee (No. 696/22).

CASE SUMMARIES

First case

A 49-years-old woman was admitted to our hospital with confirmed SARS-CoV2 infection by Polymerase Chain Reaction (PCR) test. She stated that symptoms started five days before with fever, the highest measured up to 39.9°C, and dry and irritating cough. Five days before admission to our hospital, she was treated with ceftriaxone, azithromycin, methylprednisolone, and acetylsalicylic acid at home. Laboratory findings were within referent range. Upon admission, the patient was conscious, afebrile, eupnoeic (saturation was 98% on room air), heart rate of 78 beats per minute, normally discolored skin, and visible mucous membranes with normal elasticity and turgor of the skin. Laboratory data showed high values of C reactive protein (CRP): 56.9 mg/ml, ferritin: 614 ng/ml, lactate dehydrogenase (LDH): 551 U/L, and Interleukin 6 (IL-6): 159. Other parameters were within the normal range. On the chest X-ray, bilateral interstitial pneumonia was described. During hospitalization, the patient's respiratory function was deteriorating significantly. In arterial blood gas analyses, hypoxemia was recorded with partial oxygen pressure (PaO_2: 60 mmHg) while saturation (SaO_2) was 90%. The need for oxygen support arose, initially on low flows and then on continuous positive airway pressure (CPAP). In laboratory findings, CRP was dramatically raised, 184 mg/ml, IL-6 value was 2018, ferritin 1832 ng/ml, LDH1255 U/L, and D-dimer was 728. The value of procalcitonin was 0.09 (ref. range <0.5), and presepsin 859 (high possibility of developing sepsis). Urine and blood cultures were sterile (taken on two occasions).

Due to further progression of symptoms, we opted for a chest computed tomography (CT). Chest CT showed bilateral interstitial pneumonia. It presented as moderate severity with right posterobasal acinar (bacterial origin) consolidation and ground-glass opacity (GGO) in both upper lobes. CT score was 15/25 (Figure 1). We continued treatment with ceftriaxone 2gr iv five more days, metronidazole 1.5gr iv for seven days, then we continued with meropenem 3gr iv for seven days, vancomycin 2gr iv as well for seven days, low molecular weight heparin (LMWH) 0,4ml SC. for sixteen days, favipiravir five days according to COVID19 protocol, methylprednisolone 40mg iv for three days, tocilizumab I dose (a second dose was not given due to an adverse clinical response), immunoglobulins 20mg iv, and Vitamins C and D all according to protocol. The patient was successfully discharged from the hospital with a recommendation to do a control laboratory analysis, D-dimer, X-ray examination, and a proposal to use rivaroxaban 10 mg once daily for three months.

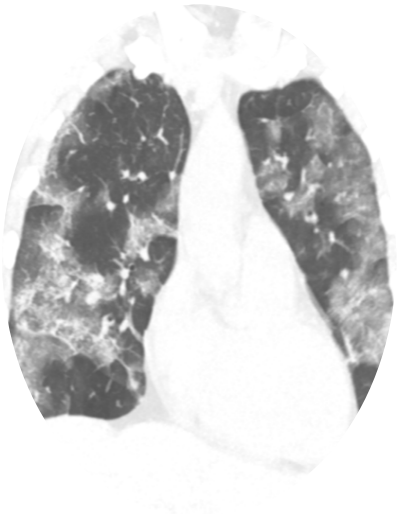

Figure 1. Chest CT shows bilateral interstitial pneumonia-medium severity with right posterobasal acinar consolidation and ground-glass opacity (GGO) in both upper lobes. CT score: 15/25

Second case

A 52-years-old man was hospitalized at our clinic due to symptoms in the form of fever and malaise. The symptoms started three days before admission in the form of fever, measured up to 38°C, and then a malaise that was presented throughout the examination. He stated that antibiotic therapy was commenced before hospitalization but did not know the names of antibiotics. PCR test was negative. Chest X-ray was normal. On physical examination, the patient was conscious, afebrile, eupnoeic, pulse oximetry saturation was 96% on room air, normally discolored skin, and visible mucous membranes with normal elasticity and turgor of the skin. During hospitalization, in laboratory findings, there was an increase of CRP (12.8 mg/ml), ferritin 403 ng/ml, LDH 688 U/L, and fibrinogen 6.34 g/l. Values of D-dimer at the beginning were within the normal range then slightly increased to 475. After admission, the patient was febrile every day, over 38°C, and respiratory function gradually deteriorated. We decided to check the values of IL-6, initially was 38,8 but rapidly increased; the highest value was 2171. However, the values of procalcitonin and presepsin excluded the possibility of sepsis. Blood cultures were sterile. The respiratory function continued to deteriorate and there was a need for non-invasive ventilation (NIV). Due to the general decline of the patient's condition and non-respondence to the medicament treatment, we opted for a chest CT. The Chest CT showed bilateral mixed severe pneumonia in progression, in both upper and medium lobes. GGO was dominant in both lower lobes and was described as crazy paving changes. The CT score was 22/25 (Figure 2).

The patient was treated with tocilizumab (II doses), ceftriaxone 2 gr iv for seven days then with meropenem 3 gr iv for ten days, vancomycin 2 gr iv for seven days, metronidazole 1,5 gr iv for seven days, LMWH 0,8 ml SC. for eighteen days, methylprednisolone 80 mg iv for ten days then 40 mg IV for eight days, and vitamins C and D according to COVID19 protocols. After the improvement of the general condition, the patient was released with advice for a control chest X-ray and laboratory examination with a proposal to use apixaban 5 mg two times daily for one month.

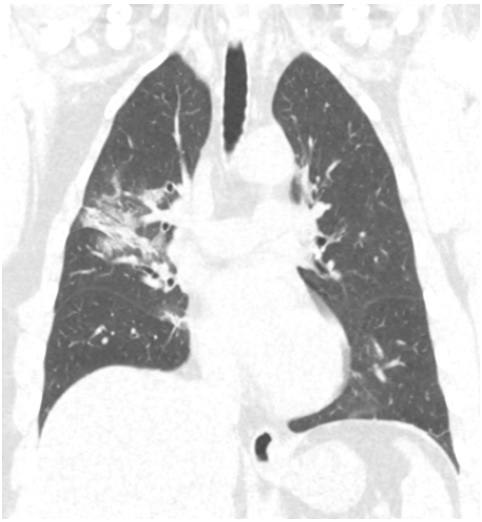

Figure 2. Chest CT shows bilateral mixed severe pneumonia in progression, in both upper lobes and medium lobe. GGO are dominant in both lower lobes describing crazy paving changes. CT score: 22/25

DISCUSSION

There is no data about the incidence of CRS in COVID-19. In some diseases like acute lymphoblastic leukemia (ALL) and lymphoma, the incidence was 16.1% between patients older than 18 years and 28.6% in patients younger than 18 (4). Fever, malaise, and dry cough were the most common symptoms of our patients. According to data from one research among 24410 adults, the most prevalent symptoms of COVID-19 were fever (78%), cough (57%), and fatigue (31%) (5). Initially, we noticed a slight increase in markers of inflammation (CRP, ferritin, LDH, and IL-6) but in the further course of hospitalization, these values were even four-digit. Are all inflammatory markers relevant in COVID-19 or do some stand out? We came across different data. One group of authors believes that serum ferritin values could be an independent risk factor for disease severity in COVID-19 while CRP and lymphocyte count were found to be two additional independent risk factors for disease severity through the multivariate logistic regression model (6).

The values of IL-6 had rapidly increased and reached values over 2000. According to the data from one meta-analytical study in which data of IL-6 values were collected in more than 9000 patients, the following results were obtained: in COVID-19 infection, IL-6 values were between the range of 21.6-62.3 pg/ml; in cytokine release syndrome (CRS) (632.3-15302.9 pg/ml), sepsis (550.1-1758.4 pg/ml) and in acute respiratory distress syndrome (ARDS) unrelated to COVID-19 (216.3-978.7pg/ml) (7).

Since the condition of our patients was deteriorating from day to day and they were constantly febrile, we decided to determine the values of presepsin, procalcitonin, and urine and blood cultures. In the first case, based on presepsin values, there was a high possibility of developing sepsis. Procalcitonin besides urine and blood cultures were within normal ranges. In the second case, the possibility of sepsis was excluded. Presepsin was found in 2004, a biomarker with high sensitivity and specificity in the diagnosis of sepsis. It is a very important biomarker to distinguish sepsis from systemic inflammatory response syndrome (SIRS). Meta-analytic studies have shown that procalcitonin and CRP are commonly used as biomarkers in the diagnosis of sepsis while assessing the severity of the infection and guiding the use of antibiotics. However, their sensitivity and specificity varied in the diagnosis of sepsis. Also, the values of IL-6 were not high and declined gradually as the time of infection extended (8). These findings singled out presepsin from other biomarkers (8).

Although only in the first case there was a PCR test-proven infection, changes in chest CT which described bilateral pneumonia, consolidations, GGO, and crazy paving changes could be good indicators of COVID-19 infection. In one study, 96 patients participated with proven COVID-19 infection. They were divided into two groups: first where the CT was done in the first week after onset of symptoms, and the second group where CT was done in the second week after onset of symptoms. The chest CT results were similar to ours: GGO was noted in 94.3% in the first and in 88.5% in the second group, consolidations (25.7% vs. 34.6%), the crazy paving (15.7% vs. 3.8%), and cavitation 1.4% only in the first group (9).

We started treatment with third-generation cephalosporins and then we continued with carbapenems, glycopeptides, nitroimidazole, anti-IL-6 inhibitor, LMWH, glucocorticoids, immunoglobulins (IVIG), and vitamins. Some authors noticed that glucocorticoids are the most prescribed medications in COVID-19 (72% in the intensive care units) but we have to use them carefully in viral infection because some researchers have reported inferior results in SARS patients treated with them due to delayed purging of the virus. IVIG and plasma from recovered patients were very useful in individuals with weakened immune systems. IVIG can block various proinflammatory cytokines, Fc receptors, and leucocytes adhesion molecules by suppressing Th1 and Th17 cell subtypes and neutralizing pathogenic autoantibodies.

The use of LMWH affected a lower mortality rate (40%) compared to patients who did not use this therapy (64%) (10). Tocilizumab, the antagonist of IL-6R seems to be the treatment of choice for patients with CRS. Some studies showed that the use of Tocilizumab can improve outcomes of patients with severe or critical COVID-19 infection (11). We could not find data on the importance of antibiotic use in CRS COVID-19 patients but we believe that they played important role in improving the clinical condition of our patients. On discharge, patients were advised to use oral anticoagulation therapy (rivaroxaban and apixaban) for a certain period. In one cohort study, authors noticed that treatment with both direct oral anticoagulants or Vitamin K antagonists was associated with improved outcomes (12).

CONCLUSION

CRS is a complex syndrome that significantly complicates the clinical picture and treatment outcome of hospitalized COVID-19 patients. The presented patients had a significant complication of the clinical condition from the moment of hospitalization until discharge. We had suspected that they had developed sepsis, but the rise

in IL-6 levels made us suspect that it was actually the development of CRS. It is important to focus on educating doctors about this syndrome and developing medications that can decrease inflammation in individuals who already have the disease.

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