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Protracted or recurrent COVID-19 associated cytokine storm in a patient with chronic lymphocytic leukemia receiving rituximab-based chemotherapy

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ABSTRACT

A 52-year-old male patient who was diagnosed with chronic lymphocytic leukemia two years ago; admitted to our hospital with complaints of fever (>38°C), shortness of breath, and fatigue. He was receiving fludarabine, cyclophosphamide, and rituximab (FCR) regimen for one year after two courses of cyclophosphamide, vincristine, and prednisolone (CVP) regimen. The patient was diagnosed with COVID-19 associated cytokine storm and tocilizumab 800 mg was administered in addition to corticosteroids.

Significant improvement was observed in both clinical and laboratory parameters and his hypoxemia resolved. The patient whose complaints recurred on the 13th day of discharge was admitted to the hospital again with severe hypoxemia (oxygen saturation < 90) and fever (>38°C). Pulse steroid (250 mg methylprednisolone for three days, followed by 40 mg/day) and anakinra 400 mg/day intravenously were started.

Despite the treatment, the patient progressed to respiratory failure and died on the sixth day of second hospitalization.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an illness caused by SARS-CoV-2 and has led to significant morbidity and mortality globally, since its first appearance in China in December 2019 [1]. Presentations of COVID-19 range from asymptomatic/mild disease to severe viral pneumonia. Recent evidences had shown worse outcome of COVID-19 in patients with cancer [2]. Hyperinflammation manifesting as a cytokine storm is one of the most frequent findings of COVID-19 [3], therefore rheumatologists had a crucial role in management of disease.

Herein, we aimed to present a case of protracted/recurrent COVID-19 associated cytokine storm in a patient with chronic lymphocytic leukemia who received rituximab-based chemotherapy. Patient consent was obtained for this paper.

2. Case report

A 52-year-old male patient who was diagnosed with chronic lymphocytic leukemia two years ago; admitted to our hospital with complaints of fever (>38°C), shortness of breath, and fatigue. He was receiving fludarabine, cyclophosphamide, and rituximab (FCR) regimen for one year after two courses of cyclophosphamide, vincristine, and prednisolone (CVP) regimen. His last FCR treatment was four months ago. COVID-19 RT-PCR was positive and thorax CT revealed extensive ground glass opacities compatible with severe COVID-19 pneumonia Fig. 1. It was learned that he was hospitalized for six days due to COVID-19 one year ago before initiation of FCR treatment, but he did not need oxygen support or an intensive care unit admission. He also denied COVID-19 vaccination during this period. Laboratory findings revealed leucocyte: 6290 10⁹/L (4000–10,000 10⁹/L), lymphocyte:360 10⁹/L, hemoglobin: 9 g/dL (12–16 g/dL), total leukocyte:15400 10⁹/L (10⁸.4 × 10⁹ 10⁹/L), INR:1.26 (0.8–1.2), ALT:71 IU (<50 IU), AST:29 IU (<50 IU), creatinine:0.6 mg/dL (0.5–0.95 mg/dL), C-reactive protein (CRP):165 mg/L (<5 mg/L), ferritin:1620 ng/mL (11–306 ng/mL), procalcitonin:0.4 ng/mL (<0.25 μg/mL), D-dimer:933 μg/mL (<520 μg/mL).

The patient was diagnosed with COVID-19 associated cytokine storm and tocilizumab 800 mg was administered in addition to corticosteroids (250 mg methylprednisolone [MP] for 3 days and followed by 40 mg/day) at 14th day of admission. Significant improvement was observed in both clinical and laboratory parameters.

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(lymphocyte: 1210 $10^9$/L, CRP < 1 mg/L, ferritin: 321 ng/mL) and his hypoxemia resolved. The patient was discharged on the 20th day with 32 mg/day MP and 4 mg/week tapering course. The patient whose complaints recurred on the 13th day of discharge was admitted to the hospital again with severe hypoxemia (oxygen saturation < 90) and fever (> 38°C). PCR test was positive and typical findings of COVID-19 was present in thorax CT (Fig. 2). Laboratory results were compatible with cytokine storm (Fig. 3) as lymphocyte: 560 $10^9$/L, ferritin: 722 ng/mL, CRP: 103 mg/L, procalcitonin: 0.1 ng/mL. Pulse steroid (250 mg methylprednisolone for three days, followed by 40 mg/day) and anakinra 400 mg/day intravenously were started due to the low availability of tocilizumab into this period, and anakinra doses increased 800 mg/day gradually. Despite the treatment, the patient progressed to respiratory failure and died on the sixth day of second hospitalization.

3. Discussion

It has been shown that COVID-19 is associated with high mortality in patients receiving rituximab due to rheumatologic diseases or hematological malignancies [4] [5]. In COVID-19 associated cytokine storm, this perturbation is initiated via attachment of the SARS-CoV-2 spike protein to its receptor, ACE2, leading hyperactivation of NF-$\kappa$B by IL-6 STATs axis [6]. A preliminary result in early months of the pandemic revealed higher IL-6, IL-8 and TNF alpha but not IL-1 beta levels in deceased patients compared to others, supports the driver role of IL-6 rather than IL-1 in the pathogenesis of severe COVID-19 [7]. The mechanism of cytokine storm in patients received immunosuppressives such as rituximab is probably due to impaired viral clearance as well as persistence of viral RNA leading to systemic inflammation after insufficient antibody response to SARS-CoV-2 [8]. Although prolonged PCR positivity as well as prolonged pneumonia is well known, there is little evidence with protracted/recurrent cytokine storm in these patients [9]. In our patient, there was a period of time with the patient’s clinical and laboratory findings completely returned to normal after discharge, suggesting that it was recurrent rather than protracted cytokine storm, although it is difficult to completely distinguish between two situations. Clinicians should be alert for protracted/recurrent COVID-19-associated cytokine storm, especially in patients receiving rituximab and/or other chemotherapies.

The safety and efficacy of tocilizumab was established in the treatment of CAR-T cell associated cytokine release syndrome and approved by FDA for this indication [10]. Moreover, higher efficacy of tocilizumab in patients with severe COVID-19 was shown in previous studies [11, 12]. These studies emphasize the crucial role of tocilizumab in hyperinflammatory syndromes including COVID-19 associated cytokine storm. Although JAK inhibitors have become an emerging therapeutic option in COVID-19-associated cytokine storm [13], we preferred anakinra over JAK inhibitors due to its higher safety profile particularly in patients with malignancy and higher infection as well as thrombosis risk. The initial dramatic response to tocilizumab in our patient and failure of anakinra treatment afterwards, may be interpreted as superiority of tocilizumab over anakinra in patients with malignancy or inflammatory diseases who developed cytokine storm while on immunosuppressive treatment. Significant changes in the immunological pathway and cytokine profile in patients receiving rituximab may have caused the remarkable difference in the treatment response between the two drugs in the patient. On the other hand, these patients should be followed-up closely for a while even a good response was achieved and extension of the treatment duration could be preferred to prevent recurrence.

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Availability of data and material

Datasets of the study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Key messages

Protracted/Recurrence of cytokine storm may occur in COVID-19, especially in patients on immunosuppression. Tocilizumab may be preferred over anakinra in these patients.

Author contribution

Contributor MB was responsible for the organization and coordination of the trial. GO was the chief investigator and responsible for the data analysis. MB and GO developed the trial design. All authors contributed to the writing of the final manuscript. All members of the MB and GO Study Team contributed to the management or administration of the trial.

Fig. 1. Bilaterally ground-glass opacities compatible with COVID-19.

Fig. 2. Bilaterally new developing ground-glass opacities and consolidation compatible with COVID-19.
Declaration of Competing Interest

Authors declare no conflicts of interest.

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