Case Presentation

Convalescent plasma therapy in aHUS patient with SARS-CoV-2 infection

Emma Diletta Stea*, Virginia Pronzo, Francesco Pesce, Marco Fiorentino, Adele Mitrotti, Vincenzo Di Leo, Cosma Cortese, Annalisa Casanova, Sebastiano Nestola, Flavia Capaccio and Loreto Gesualdo

Department of Emergency and Organ Transplantation, Nephrology, Dialysis and Transplantation Unit, University of Bari, Bari, Italy

Summary

Endotheliosis, thrombotic microangiopathy and complement system over activation have been described as pathologic features of tissue damage in the setting of coronavirus disease. Interestingly, complement-mediated cell injury is also a typical feature of atypical Hemolytic Uremic Syndrome. Indeed, a growing body of literature has described a higher risk of microangiopathy recurrence, in aHUS patients who test positive for SARS-CoV-2. The correct clinical and therapeutic management patients with a history of HUS and SARS-CoV-2 infection is not well established.

We report a case of SARS-CoV-2 infection in an aHUS patient who did not develop a recurrence of the disease and that was successfully treated with convalescent immune plasma therapy.

Introduction

Endotheliosis has been described as a pathologic feature of organ damage in the setting of coronavirus disease 2019 (SARS-CoV-2) [1]. The involvement of complement system in the endothelial cell damage and in the pathogenesis of SARS-CoV-2 disease has also been highlighted. Complement mediated endothelial-cell activation and injury, is a hallmark of atypical Hemolytic Uremic Syndrome (aHUS) [2]. On this premise, patients with aHUS history who test positive for SARS-CoV-2 have a higher risk of microangiopathy recurrence. We report the second case of SARS-CoV-2 infection in a patient with a history of aHUS who did not develop microangiopathy and was successfully treated with convalescent immune plasma therapy.

Statement of ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The study did not require a formal approval from the ethics committee according to the Italian law since it was performed as a retrospective description of a clinical case in the context of normal clinical routines (art.1, leg. decree 211/2003). However, it was performed according to the guidelines of the Declaration of Helsinki. Data were previously anonymized, according to the requirements set by Italian Data protection Code (leg. Decree 196/2003).
an efficient respiratory profile with normal blood gas analysis results (pH: 7.44, pCO2: 36 mmHg, pO2: 77 mmHg, P02/FiO2 = 376). Inflammatory markers were moderately increased (C-reactive protein 23.4 mg/l, D-dimer 235 µg/L and interleukin-6 50.6 pg/ml), showing a clinically mild form of SARS-CoV-2. Since the admission, the patient received azithromycin 500 mg per os (once daily for 2 weeks), i.v. dexamethasone (6 mg once daily for 16 days followed by a fast tapering) and s.c. enoxoparin (4000 UI/daily for 50 days).

During the following two weeks, her clinical condition progressively worsened, as she presented dry cough, shortness of breath, and a substantial decrease in Oxygen Saturation down to 89%. The respiratory failure required Venturi masks (FiO2 60%), followed by Continuous Positive Airway Pressure (CPAP) with maximization of FiO2 (100%) and of Positive End Expiratory Pressure (PEEP) (10 cmH2O). Laboratory tests showed a severe increase of inflammatory markers (Figure 1A). Chest X-ray revealed signs of polysegmental bilateral viral pneumonia with multiple ground glass opacity areas (Figure 2A).

At the onset of respiratory symptoms, Ceftriaxone 2 g i.v. (once daily for 16 days) was added to prevent bacterial co-infection. Despite such treatment, the clinical worsening required intensive care unit (ICU) support. Therefore, we decided to start a rescue therapy with three doses of fresh frozen plasma (250 ml for each dose) obtained from a SARS-CoV-2 convalescent patient, according to the Tsunami Protocol. After the second plasma infusion, blood gas analysis revealed an improvement of PO2/FiO2 ratio: from 84, at the beginning of the therapy, to 224 on the 3rd day of plasma administration without other ventilation change. The PO2 - FiO2 ratio showed a slightly decrease between the days 10th - 20th of November corresponding to a gradually ventilator weaning and the recovery of the spontaneous breathing.

Hyper-immune Plasma (HP) has been successfully used in several viral epidemics such as SARS, MERS, and Ebola [3]. Given this evidence, HP has also been administered to some SARS-CoV-2 patients. The World Health Organization (WHO) allowed the CP treatment for «serious diseases for which there

Inflammatory markers improved and the chest X-ray showed a resolution of SARS-CoV-2 pneumonia (Figure 2C). Hence, 55 days after the SARS-CoV-2 diagnosis, she was discharged.

Discussion

Hyperimmune Plasma (HP) has been successfully used in several viral epidemics such as SARS, MERS, and Ebola [3]. Given this evidence, HP has also been administered to some SARS-CoV-2 patients. The World Health Organization (WHO) allowed the CP treatment for «serious diseases for which there
Convalescent plasma therapy in aHUS patient with SARS-CoV-2 infection

are no effective pharmacological treatments». Nevertheless, the literature has showed contrasting results regarding the benefit of plasma therapy in SARS-CoV-2 patients and there is no recommendation on which type of patient HP should be administered. This case provide evidence that HP therapy can be considered as a rescue therapy in patients with aHUS history and moderate- to severe SARS-CoV-2 infection within 14 days of onset, maintaining a safety profile and without the risk of aHUS relapse.

Some reports showed the utility of HP therapy in SARS-CoV-2 patients, especially if it is administrated during the stage of viral replication [3]. The efficacy has been demonstrated mainly in sickly patients with a severe immunodeficiency, which had a relatively lower viral clearance and later antibody response [4].

Though aHUS patients are not immunodeficient, they seem to be exposed to higher risk of thrombotic event and recurrence of HUS [5].

Coronavirus 19 induces a direct endothelial damage and an alternative pathway complement (APC) activation through the SARS-CoV-2 spike surface protein [6]. The complement activation amplifies the endothelial injury, mainly in subjects with a genetic defect in the complement regulation, exposing aHUS patients with SARS-CoV-2 to a higher risk of microangiopathy. Therefore, the management of these sickly patients must be prompt to reduce the additional complications triggered by complement activation. In literature, some cases [5,8] of aHUS patient who developed disease recurrence triggered by SARS-CoV-2 infection has been described. Only in one aHUS patient HP has been administered, during the worsening of COVID pneumonia, with successful outcome [9]. That patient did not require mechanical ventilation and did not have a known complement genetic variant neither aHUS recurrence history [9]. In contrast, our patient developed a severe form of SARS-CoV-2 pneumonia, requiring mechanical ventilation and ICU support. Considering the high susceptibility of our patient to HUS recurrence and the critically worsening respiratory function, we decided to administer HP as rescue therapy. Our patient had a good response to the HP treatment, which also showed a favorable safety profile. Moreover, she had no HUS recurrence, maybe because HP may reduce the viral replication.

In conclusion, our observation, although limited to a single patient, shows that HP can be considered as rescue therapy in patients with moderate-severe SARS-CoV-2 infection and aHUS history, and does not increase the risk of microangiopathy recurrence.

Author Contributions: E.D. Stea wrote the manuscript with support from F. Pesce. V. Pronzo collected the data and designed the figures. All authors provided critical feedback and helped shape the analysis and manuscript. L. Gesualdo supervised the project. Finally, all the authors define the therapy and the medical care of the patient during the job in the Nephrology COVID Unit of Bari.

Data availability statement: All data generated during this study are included in this article. Further enquiries can be directed to the corresponding author.

Disclosure: the authors declare no conflict of interest.

References

1. Noris M, Benigni A, Remuzzi G. The case of complement activation in COVID-19 multiorgan impact. Kidney Int. 2020; 98: 314-322. PubMed: https://pubmed.ncbi.nlm.nih.gov/32461141/

2. Zipfel PF, Wiech T, Stea ED, Skerka C. CFHR Gene Variations Provide Insights in the Pathogenesis of the Kidney Diseases Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy. J Am Soc Nephrol. 2020; 31: 241-256. PubMed: https://pubmed.ncbi.nlm.nih.gov/31980588/

3. Petruungaro A, Quartarone E, Sciarrone P. Anti-SARS-CoV-2 hyperimmune plasma workflow. Transfus Apher Sci. 2020; 59: 102850. PubMed: https://pubmed.ncbi.nlm.nih.gov/32540345/

4. Cusi MG, Conticini E, Gandolfo C, Anichini G, Savellini GG, et al. Hyperimmune plasma in three immuno-deficient patients affected by...
non-severe, prolonged COVID-19: a single-center experience. BMC Infect Dis. 2021; 21: 630.
PubMed: https://pubmed.ncbi.nlm.nih.gov/34210259/

5. Ville S, Le Bot S, Chapelet-Debout A, Blancho G, Fremeaux-Bacchi V, et al. Atypical HUS relapse triggered by COVID-19. Kidney Int. 2021; 99: 267-268.
PubMed: https://pubmed.ncbi.nlm.nih.gov/33188793/

6. Yu J, Yuan X, Chen H, Chaturvedi S, Braunstein EM, et al. Direct activation of the alternative complement pathway by SARS-CoV-2 spike proteins is blocked by factor D inhibition. Blood. 2020; 136: 2080-2089.
PubMed: https://pubmed.ncbi.nlm.nih.gov/32877502/

7. Maharaj N, Sankat S, Spann J, Goorachan S, Sookoo A. POS-041 Haemolytic Uremic Syndrome (HUS) with Covid-19 infection: 2 case reports. Is there a direct link? Kidney Int Rep. 2021; 6: S18–19.
PubMed: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8049736/

8. Jhaveri KD, Meir LR, Flores Chang BS, Parikh R, Wanchoo R, et al. Thrombotic microangiopathy in a patient with COVID-19. Kidney Int. 2020; 98: 509-512.
PubMed: https://pubmed.ncbi.nlm.nih.gov/32525010/

9. Trimarchi H, Gianserra R, Lampo M, Monkowski M, Lodolo J. Eculizumab, SARS-CoV-2 and atypical hemolytic uremic syndrome. Clin Kidney J. 2020; 13: 739-741.
PubMed: https://pubmed.ncbi.nlm.nih.gov/33117528/