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Case Report

Combination of thrombolytic and immunosuppressive therapy for coronavirus disease 2019: A case report

Panagiotis Papamichalis[a,*], Antonios Papadogoulas[a], Periklis Katsiafylloudis[a], Apostolia-Lemonia Skoura[a], Michail Papamichalis[b], Evangelia Neou[a], Dimitrios Papadopoulos[a], Spyridon Karagiannis[a], Tilemachos Zafeiridis[a], Dimitris Babalis[c], Apostolos Komnos[a]

[a] Intensive Care Unit, General Hospital of Larissa, Larissa, Greece
[b] Cardiology Department, University General Hospital of Larissa, Larissa, Greece
[c] Emergency Department, General Hospital of Larissa, Larissa, Greece

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ABSTRACT

In a proportion of patients, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a multisystem syndrome characterized by hyperinflammation, acute respiratory distress syndrome (ARDS), and hypercoagulability. A 68-year-old man with coronavirus disease 2019 (COVID-19) was admitted to the intensive care unit with respiratory failure, cytokine release syndrome (CRS), and skin ischemia – microthrombosis. Specific coagulation and inflammatory markers (D-dimer, ferritin, and C-reactive protein), along with the clinical picture, triggered the trial of recombinant tissue plasminogen activator (rt-PA) and tocilizumab. This was followed by resolution of the skin ischemia and CRS, while respiratory parameters improved. No major complications associated with rt-PA or tocilizumab occurred. The combination of rt-PA with targeted anti-inflammatory treatment could be a new therapeutic option for patients with COVID-19, ARDS, hyperinflammation, and increased blood viscosity.

1. Introduction

A 68-year-old man presented to the emergency department of the General Hospital of Larissa complaining of a high-grade fever for the last 10 days. He had been taking a broad-spectrum antibiotic (clarithromycin) and an antiviral drug (oseltamivir) for 3 days prior to his admission, with no improvement. His medical history included hypertension and well-controlled type 2 diabetes mellitus, under treatment with oral anti-diabetic agents. Arterial blood gases revealed acute hypoxemic (type I) respiratory failure. Multiple diffuse infiltrates on both lungs were apparent in his chest X-ray. A pharyngeal swab was taken and real-time PCR was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), confirming coronavirus disease 2019 (COVID-19) (World Health Organization, 2020).

2. Case report

The patient was intubated a few hours after his admission due to worsening of respiratory failure, fulfilling the criteria for moderate acute respiratory distress syndrome (ARDS) (Ranieri et al., 2012) (arterial blood gas oxygen tension (PaO_2)/fraction of inspired oxygen (FiO_2) (P/F) ratio 115 mmHg, with positive end-expiratory pressure of 8 cmH_2O). His clinical features, laboratory tests, and calculated HScore (value 239) were compatible with cytokine release syndrome (CRS) (Fardet et al., 2014). His medications included hydroxychloroquine, azithromycin, a broad-spectrum antibiotic (meropenem), and standard care for critically ill patients. From day 3 to day 10 of hospitalization, he received anakinra, a rheumatology drug that blocks the biological activity of interleukin 1, at a dose of 200 mg three times a day, with a transient laboratory (lowering of ferritin; Table 1) and clinical (P/F ratio 241 mmHg) response.

Thirteen days after his admission and 3 days after anakinra was discontinued, the patient presented a significant deterioration with respiratory worsening (P/F ratio 158 mmHg). His upper and lower extremities became cold, with extreme prolongation of the capillary refill time, and he developed signs of ischemia with dark

* Corresponding author. Intensive Care Unit, General Hospital of Larissa, Tsakalof 1, 41221 Larissa, Greece. Tel.: +30-241350-4-415; fax: +30-241-0-532787.
E-mail address: ppapamih@med.uth.gr (P. Papamichalis).

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Table 1
D-dimer, ferritin, and C-reactive protein levels measured during the patient's hospitalization

	Day from admission								
	1	3[a]	6	8	10[b]	12	13[c]	35	40
D-dimer (μg/ml)	1.9	2.1	2.8	2.6	4.6	4.9	9.8	2.6	2.7
Ferritin (ng/ml)	>10 000	>10 000	7380	3185	3000	2820	3850	655	844
C-reactive protein (mg/l)	170	165	101	127	151	164	179	19	11

[a] Anakinra initiation.
[b] Anakinra cessation.
[c] Day of deterioration and recombinant tissue plasminogen activator (rt-PA)/tocilizumab administration.

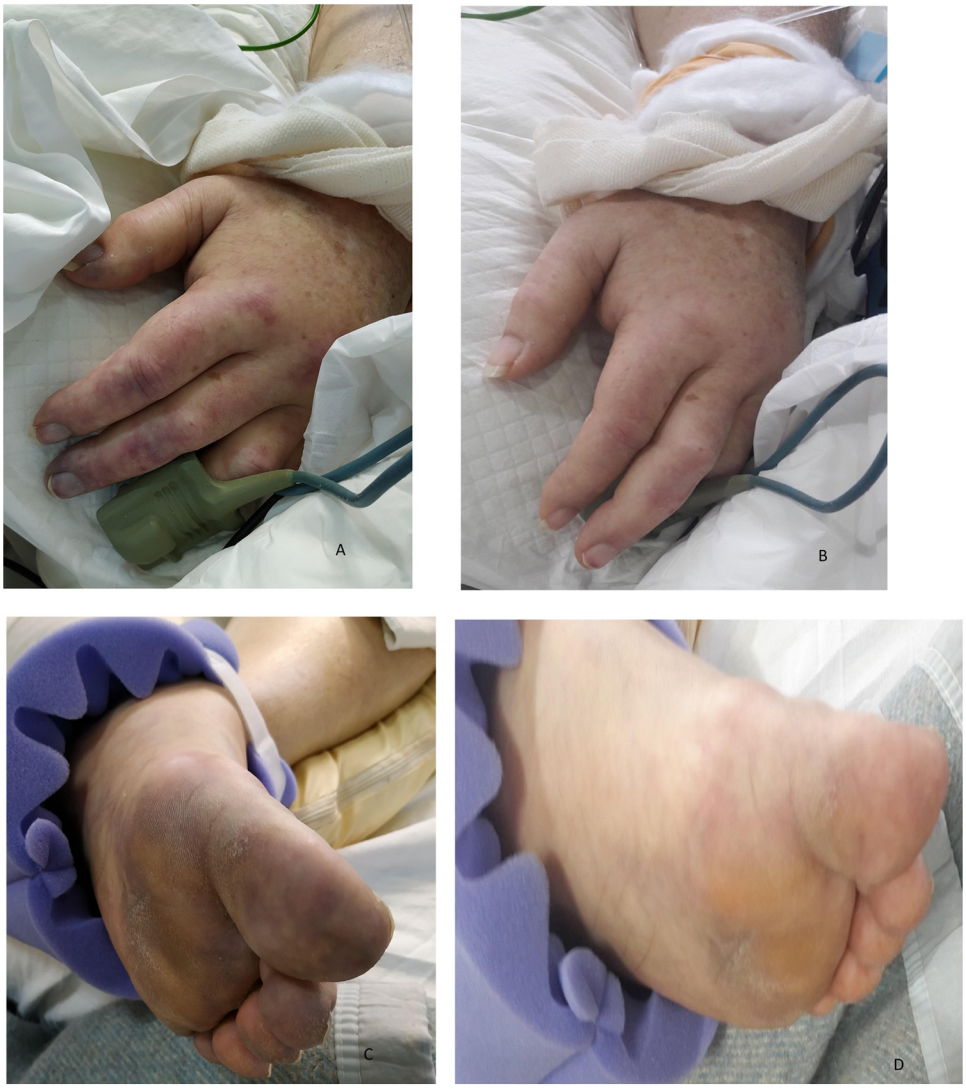

Fig. 1. The patient's left hand (A) before administering recombinant tissue plasminogen activator (rt-PA)/tocilizumab, and (B) after 12 hours of continuous rt-PA infusion and 2 hours of tocilizumab administration, with resolution. The patient's left foot (C) before administering rt-PA/tocilizumab, and (D) after 12 hours of continuous rt-PA infusion and 2 hours of tocilizumab administration, with resolution.

hypoperfused regions (Fig. 1A, C). A pulse could be detected upon carotids, femoral, brachial, and radial arteries, but pulse oximetry tested on all digits of the hands and feet could not measure oxygen saturation (SO_2). Ultrasound and Doppler examinations were negative for large vessel occlusions. Cardiac echo showed preserved systolic function of both ventricles (ejection fraction of the left ventricle 60%), with a moderately dilated right ventricle (finding stable compared with the previous days), but no signs compatible with pulmonary embolism and no evidence of endocarditis.

Another alarming observation was the patient's D-dimer levels. These increased slowing during his hospitalization, but on the day of deterioration they presented a peak, reaching almost double the value of the previous day, 9.8 μg/ml from 4.9 μg/ml (upper normal limit 0.5 μg/ml) (Table 1). Ferritin (increase to 3850 ng/ml from 2820 ng/ml) and C-reactive protein (CRP) (increase to 179 mg/l from 164 mg/l) values showed an elevation as well (Table 1).

Two therapeutic actions were performed: (1) thrombolysis with recombinant tissue plasminogen activator (rt-PA) according to a salvage protocol proposed in a recent publication (Moore et al.,

2020). In a patient weighing 100 kg, we administered 25 mg of rt-PA over 2 hours, followed by 25 mg of rt-PA infused over the subsequent 22 hours. Therapeutic administration of low-molecular-weight heparin (LMWH), enoxaparin, with monitoring of anti-Factor Xa activity (target range 0.6–1 IU/ml) was applied after rt-PA infusion. (2) Eight hours later we administered 400 mg of tocilizumab, a recombinant humanized anti-human interleukin 6 receptor monoclonal antibody with good preliminary results for patients with COVID-19 (Xiaoling et al., 2020); this was infused over a period of 2 hours.

Twelve hours after the initiation of rt-PA with its continuous infusion running and 2 hours after the completion of tocilizumab infusion, the patient's cutaneous and subcutaneous areas of ischemia resolved (Fig. 1B, D). His extremities became warm, the capillary refill time returned to normal, and a pulse oximeter could measure SO_2 again. We also observed an improvement in P/F ratio, which reached 228 mmHg at 15 hours after rt-PA initiation and 5 hours after tocilizumab infusion. No complication regarding rt-PA occurred and only neutropenia was observed, which was attributed to tocilizumab and was easily reversed with one dose of filgrastim, a bone marrow-stimulating factor for white blood cell production.

The improvement in respiratory parameters lasted only 48 hours. Afterwards, the P/F ratio fell to values below 150 mmHg with no response to neuromuscular blockade or recruitment manoeuvres. Prone positioning was applied according to international protocols (World Health Organization, 2020), with a moderate response. However no signs of cutaneous/subcutaneous ischemia appeared again, while CRS clinical and laboratory findings resolved.

After 35 days of hospitalization, PCR examination for SARS-CoV-2 remained positive and it was decided to transfuse convalescent plasma. The patient was negative for the detection of the virus 5 days later. D-dimer, ferritin, and CRP values remained low for many days (Table 1). Due to the sustained thrombocytopenia and anaemia, despite the patient's improvement in the other laboratory parameters, a bone marrow aspiration was performed. The results were compatible with a diagnosis of acute myeloid leukaemia (AML). On day 45, the patient became septic and presented severe deterioration. Finally he died due to candidaemia and *Pseudomonas aeruginosa* bacteraemia.

3. Discussion

Pathological changes observed in the lungs of patients with COVID-19 include the deposition of fibrin in the airspaces and lung parenchyma and the formation of microthrombi in vessels. These changes are identical to those in the lung of patients with ARDS of other aetiologies (MacLaren and Stringer, 2007). However, in patients with ARDS and COVID-19, the thrombotic element is enhanced, with many recent reports of confirmed pulmonary embolism in COVID-19 patients (Danzi et al., 2020; Poggiali et al., 2020). The spectrum of thrombotic events apart from pulmonary embolism may include microthromboses in the pulmonary vasculature causing a slower and more dangerous deterioration. The same concept has already been proposed for the pathogenesis of another severe viral infection, influenza pneumonia (Yang and Tang, 2016).

The coupling of inflammation and coagulation is well known and has been described in the international literature (MacLaren and Stringer, 2007; Terpos et al., 2020). These procedures share common molecular pathways and interact with each other, and many times this interaction leads to the enhancement of inflammation and finally to damage to the host. Although our patient did not have a disseminated intravascular coagulation (DIC) compatible score (Taylor et al., 2001), his skin manifestations were very similar to those of DIC, which is very common amongst critically ill COVID-19 patients (Terpos et al., 2020). Endothelial cell activation/damage due to the virus binding to the ACE2 receptor, immune deregulation, and endothelial dysfunction are proposed mechanisms for DIC in COVID-19. This 'immunothrombosis' process (Terpos et al., 2020) could respond well to an immunosuppressive/thrombolytic combination therapy like the one we used. We believe that both drugs contributed to the patient's improvement.

One basic trigger for our decision to administer rt-PA and tocilizumab was the elevation of D-dimer, ferritin, and CRP values. Indeed reports have indicated that an increase in D-dimer is not only a marker of severe disease, but is also a prognostic marker of deterioration (Terpos et al., 2020; Lippi and Favaloro, 2020). Daily monitoring of D-dimer is proposed by the international literature and could serve as an indicator of the time-point at which an intervention with rt-PA/tocilizumab should be considered. Simultaneous elevations of ferritin and CRP should enhance the level of alertness for D-dimer elevation.

Moore et al. (2020) propose unfractionated heparin infusion after rt-PA. We applied LMWH at a therapeutic dose instead. This choice was based on certain advantages that LMWH presents: a smaller risk of heparin-induced thrombocytopenia than unfractionated heparin, good safety profile, and correlations of its use with decreased mortality (Tang et al., 2020) and potential anti-inflammatory effects (Liu et al., 2020) in COVID-19 patients.

The diagnosis of AML explained our patient's final deterioration despite our intense efforts; however AML had no clear clinical correlation with the emergence of CRS. CRS represents a serious side effect of T-cell redirecting therapies in haematological malignancies like AML (Jacobs et al., 2018), but there is no report of CRS occurring in patients with AML who have received no therapy. Thus we believe that CRS was solely a COVID-19 manifestation.

Although considerable experience with tocilizumab alone exists, to our knowledge this is the first report on the use of a combination thrombolytic and anti-inflammatory therapy for COVID-19 in the international literature. The results of rt-PA/tocilizumab administration were promising as this led to transient respiratory stabilization and full resolution of the CRS and skin manifestations. Our hope is that our experience with rt-PA/tocilizumab will help towards understanding of COVID-19 and saving other patient lives.

Declarations

Sources of funding: None to declare.

Ethical approval and consent to participate: The patient's family signed the consent form for his clinical information and images to be reported and potentially published (the patient was under sedation and died). This case report was approved by the institutional review board of our hospital, approval number 47 (16/04/2020).

Conflict of interest: None to declare.

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