IDCases 22 (2020) e00946

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case report

A case of corticosteroid-responsive SARS-CoV-2 related massive rhabdomyolysis

Maria Cunha[a,*], Inês Pinho[b], Marta Lopes[c], Frederico Trigueiros[c], Sandra Braz[c], Fábio Medeiros[a]

[a] Department of Infectious Diseases at the Santa Maria Hospital, Centro Hospitalar Universitário Lisboa Norte, Hospital De Santa Maria; Serviço De Doenças Infecciosas, Avenida Professor Egas Moniz 1649-035 Lisboa in Lisbon, Portugal
[b] Department of Oncology at the Santa Maria Hospital, Centro Hospitalar Universitário Lisboa Norte, Hospital De Santa Maria, Serviço De Oncologia, Avenida Professor Egas Moniz 1649-035, Lisboa in Lisbon, Portugal
[c] Department of Internal Medicine at the Santa Maria Hospital, Centro Hospitalar Universitário Lisboa Norte, Hospital De Santa Maria, Serviço De Medicina II, Avenida Professor Egas Moniz 1649-035 Lisboa in Lisbon, Portugal

ARTICLE INFO

Article history:
Received 26 July 2020
Received in revised form 31 August 2020
Accepted 1 September 2020

Keywords:
COVID-19
SARS-CoV-2
Corticosteroids
Rhabdomyolysis
Systemic inflammatory response syndrome

ABSTRACT

The 2019 coronavirus pandemic has united scientific and medical communities in a worldwide quest for understanding the pathophysiology of this rapidly spreading disease in order to develop effective treatments. We present a case of a 46-year-old woman with breast cancer who was found positive for SARS-CoV-2 in a screening test and developed massive rhabdomyolysis (creatinine kinase 87,456 U/liter) as well as new-onset lymphopenia and signs of lung disease starting on the 16th day of clinical surveillance, one month after the last administration of chemotherapy. Nasopharyngeal swab was still positive for SARS-CoV-2 RNA and serology revealed antibody response against the virus.

Considering the possibility of a systemic inflammatory response in the setting of post-chemotherapy immune reconstitution, we avoided aggressive fluid administration and initiated treatment with methylprednisolone and hydroxychloroquine, resulting in rapid clearance of pulmonary infiltrates and creatinine kinase.

Complete resolution after corticosteroid treatment may provide clinicians with a viable treatment option in similar situations and adds to the growing body of evidence pointing to dysregulated immune response as a major contributing factor to disease severity.

Introduction

In March 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak a pandemic. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a betacoronavirus. [1] Pneumonia represents the most frequent and recognizable complication of SARS-CoV-2 infection, however a growing number of other serious manifestations is being identified worldwide, particularly in the setting of an exuberant inflammatory response [2]. Although small elevations of creatine kinase (CK) are commonly found in COVID-19 patients, massive rhabdomyolysis is a potentially life-threatening entity which may, if not promptly identified, lead to excess morbidity and mortality [3,4].

Here we present the first case of massive SARS-CoV-2-induced rhabdomyolysis with complete resolution after corticosteroid treatment, hoping to raise awareness for this syndrome and to provide clinicians with a viable treatment option.

Case description

We describe the case of a 46-year old woman who was diagnosed with locally invasive breast cancer in September 2019. The patient had no other known diseases or usual medication and was currently being treated with neoadjuvant chemotherapy, having received the 6th cycle of paclitaxel on April 3rd, 2020.

According to local guidelines following the outbreak of the coronavirus pandemic (SARS-CoV-2), she was subjected to a SARS-CoV-2 polymerase chain reaction (PCR) screening test

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; Il-6, interleukin 6.

* Corresponding author.
E-mail addresses: maria.r.cunha@chln.min-saude.pt (M. Cunha), ines.pinho@chln.min-saude.pt (I. Pinho), marta.l.lopes@chln.min-saude.pt (M. Lopes), frederico.trigueiros@chln.min-saude.pt (F. Trigueiros), SANDRA.BRAZ@chln.min-saude.pt (S. Braz), fabio.medeiros@chln.min-saude.pt (F. Medeiros).

https://doi.org/10.1016/j.idcr.2020.e00946

Table 1
Laboratory data. *.

	Admission	Day 16 after admission	Day 19 after admission	Day 21 after admission	Day 23 after admission	Day of discharge	1 week post discharge	Reference range †
Lymphocyte count (per mm^3)	1860	680	620	1080	1550	1340	1650	1000–4800
C-reactive protein (mg/liter)	0.9	44.8	141.0	73.0	8.2	50.3	0.8	<5
Ferritin (ng/mL)			1795	2732	1616	1179	385	13–150
Amylase (U/liter)		102	189			170	106	13–53
AST (U/liter)	14	101	442	279	57	93	16	0–32
ALT (U/liter)	16	72	216	143	96	201	47	0–33
LDH (U/liter)	173	314	2750	928	339	360	213	100–250
Creatine kinase (U/liter)			87,456	36,807	1610	534	72	26–192
D-dimer (ug/mL)	<0.15		0.54	0.36		0.66	0.24	0.0–0.25
Potassium (mmol/liter)	4.2		3.8	4.2	4.9	4.4	3.5	3.5–5.1
Creatinine (mg/dL)	0.77	1.03	0.85	0.73	0.65	0.68	0.75	0.50–0.90

(nasopharyngeal swab) prior to the following chemotherapy administration and had tested positive. She was asymptomatic and reported no recent history of fever, cough, dyspnea or gastrointestinal manifestations. She was admitted to an isolation ward in the Santa Maria University Hospital in Lisbon, Portugal, due to absence of isolation conditions at home.

Medical examination and blood tests at admittance were unremarkable (Table 1). During the first 15 days of hospital stay, the patient complained of occasional nausea and diffuse myalgia; however, beginning on May 2nd, she presented with vomiting, abdominal pain and new-onset fever. Physical examination revealed no significant findings and her oxygen saturation remained >95 %. Laboratory tests revealed *de novo* lymphopenia, slight thrombocytopenia, as well as an increase in CRP, amylase, transaminases, LDH and GGT levels. CK at the time was normal. Urine sediment analysis had unspecific alterations. An abdominal ultrasound was performed the same day, with no significant liver or biliary findings. She was given paracetamol and metoclopramide, with symptomatic relief. Over the following two days, she presented with diarrhea and a new-onset dry cough.

On May 5th, 19 days after admission, chest X-ray (Fig. 1) revealed a significant bilateral infiltrate with upper left lung consolidations. CT-scan (Fig. 2) confirmed the presence of diffuse bilateral ground-glass opacities with predominantly left lung nodular infiltrates in less than 50 % of lung parenchyma and showed no evidence of structural pancreatic disease. Blood work revealed a marked increase in CK (87,456 U/liter), LDH (2750 U/liter), ferritin (1795 ng/mL) and Il-6 (80 pg/mL), as well as further increase in CRP, transaminases, GGT, amylase and lipase. Total bilirubin, troponin, urea and creatinine remained at normal values. There was no hyperuricemia, lactic acid increase, or arterial blood gas and ion changes. Serology for SARS-CoV-2 revealed antibody response (Positive IgG: 6.92 UA/mL, equivocal IgM). Acute cytomegalovirus and Epstein-Barr virus (EBV) infections, as well as human immunodeficiency virus (HIV) and hepatitis B (HBV) infections were ruled out. Nasopharyngeal swab was still positive for SARS-CoV-2 RNA.

Other than paracetamol and metoclopramide, the patient had not been given any drugs and one month had passed since the last administration of paclitaxel. She also exhibited no muscle rigidity, hyperpyrexia, altered consciousness or autonomic instability that may have pointed to metoclopramide-induced malignant neuroleptic syndrome; nevertheless, metoclopramide was discontinued. She confirmed no personal or family history of rhabdomyolysis.

Considering the strong possibility of a cytokine-mediated response in the wake of post-chemotherapy immune reconstitution, immune-modulating therapy was proposed. According to internal guidelines, she was not eligible for tocilizumab and was administered 80 mg methylprednisolone once daily as well as hydroxychloroquine. She also received intravenous bicarbonate on the first day. In order to avoid worsening of lung disease, fluid administration was closely titrated to achieve neutral fluid balance.

Over the following 48 h, the patient experienced marked relief of myalgia, asthenia and diarrhea. Her cough became less intense and her fever resolved. Blood work showed recovery of lymphocyte counts as well as decreasing CK (36,807 U/liter), LDH, CRP and liver enzymes. Lipase and amylase remained stable. Ferritin peaked at 2753 ng/mL, beginning descent on the 3rd day of methylprednisolone. Chest x-ray showed infiltrate improvement. It was then decided to wean off methylprednisolone (10 mg decrease every 3 days, switch to oral prednisolone after 20 mg, followed by a 5 mg decrease every 3 days) and to stop hydroxychloroquine after 10 days.

Further investigation of alternative causes for rhabdomyolysis revealed normal thyroid hormone levels and a negative autoimmune myositis panel.

The patient agreed to a deltoid muscle biopsy performed after 10 days of methylprednisolone treatment. No viral RNA was detected in the muscle sample and pathology revealed no inflammatory infiltrates or signs of muscle damage.

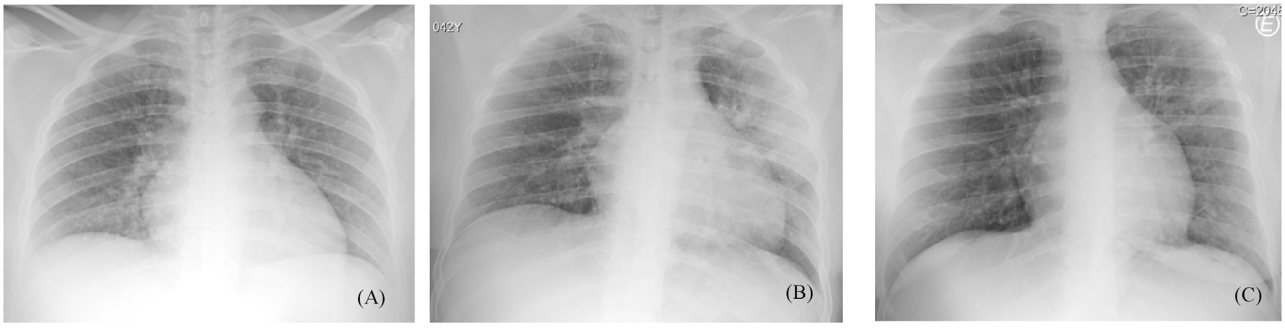

Fig. 1. Chest x-ray on admission (A); 18 days after admission (B) and 24 days after admission (C).

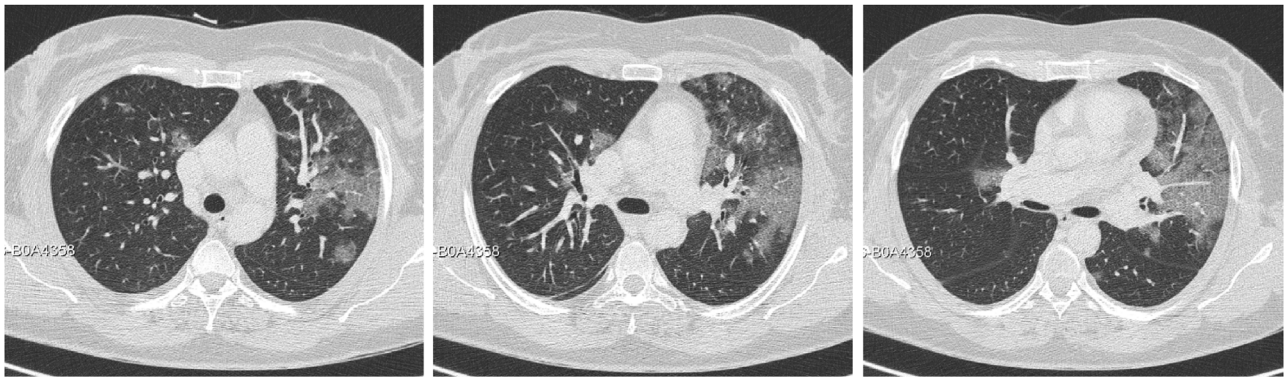

Fig. 2. Lung CT scan 19 days after admission.

The patient was discharged on the 10th day of corticosteroid treatment, having experienced no kidney damage or hypoxemia, with CK < 500 U/liter; she resumed paclitaxel administrations 10 days later, with no complications.

Discussion

Rhabdomyolysis is a clinical syndrome characterized by the rapid breakdown and necrosis of skeletal muscle cells, resulting in the leakage of potentially toxic intracellular components into the extracellular fluid. This entity ranges in severity from a mildly symptomatic illness to a potentially life-threatening condition associated with extreme CK elevation, electrolyte imbalances, myoglobinuria, acute renal failure and disseminated intravascular coagulation. [4]

Rhabdomyolysis is most frequently a result of muscle trauma; other causes include muscle enzyme deficiencies, electrolyte abnormalities, drugs, toxins, endocrinopathies and infections. Viral infections in particular have a recognized association with skeletal muscle damage, with influenza being implicated in 33 % of known viral-induced rhabdomyolysis, other common viral culprits include HIV, coxsackievirus and EBV. [4,5] Rhabdomyolysis has also been reported, albeit infrequently, with highly pathogenic human coronavirus (hCOVs) infection, such as severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS-CoV) and SARS-CoV-2. [3,6,7]

Concerning SARS-CoV-2 infection, two cases of massive non-ischemic rhabdomyolysis have been reported. The first one was described in a Chinese patient with progressive pulmonary lesions who had been medicated with lopinavir and methylprednisolone (no information about dose was provided) due to non-abatting fever. He developed rhabdomyolysis (CK levels of 11,842 U/liter) on the ninth day of hospitalization and was treated with aggressive fluid therapy, alkalinization, plasma transfusion and gamma globulin, with clinical and radiological improvement. [8]

The other case took place in New York, USA, in a patient who was admitted for rhabdomyolysis (CK of 13,581 U/liter), later being diagnosed with COVID-19. This patient was initially subjected to aggressive fluid therapy, requiring diuretics after cardiac failure exacerbation. After developing acute kidney failure, he was treated with small fluid boluses, with kidney function improvement. He was also given hydroxychloroquine for 5 days. [9]

Pathogenesis of viral-mediated rhabdomyolysis is a source of much debate; in both cases, authors underline that a final etiology for rhabdomyolysis was not established and propose that several factors may have been involved. One possible mechanism involves direct viral muscle invasion, which has been demonstrated in a few studies of rhabdomyolysis in influenza A infection. [5] Viral toxin mediated cell lysis has also been cited as a possible inducer of rhabdomyolysis, however such toxins have yet to be identified [10]. Lastly, erroneous or exaggerated immune responses resulting in collateral muscle damage seem to play a major role in most virus-induced rhabdomyolysis cases, whether by immunological cross-reactivity or virus-activated “cytokine storm syndrome”, referring to fulminant hypercytokinemia associated with multiorgan failure [5,11]. In fact, a retrospective study of COVID-19 patients found that elevated serum ferritin and IL-6 correlated with nonsurvivors [12]. Unfortunately, levels of proinflammatory cytokines are rarely measured or presented in studies on viral-mediated rhabdomyolysis.

In our particular case, the sudden onset of fever, signs of multi-organ damage, rising ferritin as well as IL-6 levels, along with the evidence of a newly acquired antibody response in a patient who had recently been cleared of immunosuppressant drugs, suggested the presence of a systemic inflammatory reaction somewhat akin to immune reconstitution inflammatory syndrome.

Although the recommended treatment of rhabdomyolysis includes aggressive fluid administration to prevent kidney lesion, we decided to avoid overhydration in an attempt to prevent further lung injury, and initiated treatment with methylprednisolone.

Corticosteroids represent a cheap, widely available and familiar form of inflammation control, yet their role in the current pandemic has proven to be a source of much debate.

Early in the outbreak, general consensus seemed to be in opposition to corticosteroid use, referencing the lack of significant clinical improvement in other virus-related acute respiratory distress syndrome (ARDS) as well as the development of serious complications and impaired clearance of SARS-CoV-2 as reasons to recommend against corticosteroid treatment. [13]

Nevertheless, as the battle against SARS-CoV-2 wages on, new publications seem to contest these initial affirmations. Citing selection bias and confounders in observational studies as possible contributing factors to any observed increased mortality in patient groups treated with corticosteroids, a Chinese expert panel concluded that the judicious use of low to-moderate doses (≤0·5–1 mg/kg per day methylprednisolone or equivalent) for a short (≤7 days) period of time did not seem to increase mortality. [14] Other recent publications have commented on the lack of evidence linking delayed viral clearance to worsened outcome in critically ill COVID-19 patients, quoting support for corticosteroid efficacy from two large studies on H1N1 and SARS (n = 7568). [15]

Wariness of corticosteroid use has been eased after the recent preliminary reports of the Randomized Evaluation of COVid-19 thERapY (RECOVERY) trial on the use of dexamethasone in hospitalized patients with Covid-19. This study, comprising of 2104 patients assigned to receive dexamethasone *versus* 4321 receiving usual care, concluded that 28-day mortality was lower among patients requiring invasive mechanical ventilation or

oxygen alone, and that the risk of progression to invasive mechanical ventilation was lower in the dexamethasone group than in the usual care group. [16] Although results of this study suggested no clear effect of dexamethasone among patients who were not receiving any respiratory support at randomization, it cannot be inferred that only patients with hypoxemia may benefit from corticosteroid use. In our case, administration of corticosteroids in the presence of radiologic evidence of lung disease and laboratory signs of a robust inflammatory reaction may have halted progression to hypoxemia.

As for the specific choice of corticosteroid, updated guidelines wishing to emulate the results of the RECOVERY trial will likely favor dexamethasone [17]; however, methylprednisolone's quicker onset, shorter duration of action and lower glucocorticoid activity compared to dexamethasone could provide a theoretical advantage, potentially lowering the risk of hypercortisolism and dysglycemia [18], a premise that warrants further investigation. Other than corticosteroids, treatment with cytokine inhibitors such as IL-6 or TNF-α receptor blockers is also being investigated [19].

Conclusion

To our knowledge, COVID-19 associated rhabdomyolysis of this magnitude has not previously been reported. After excluding other possible causes, we can attribute this finding to SARS-CoV-2 infection. Among the various possible mechanisms for virus-induced rhabdomyolysis, the sudden rise in ferritin levels and elevated Il-6, the newfound antibody response, the quick response to 80 mg methylprednisolone as well as the absence of viral RNA detected in muscle biopsy support the initial assumption that rhabdomyolysis was not a result of direct viral-mediated damage, but rather a byproduct of a hyperactive immune response.

Although myalgia and weakness are common symptoms of COVID-19, clinicians should be aware that rhabdomyolysis may occur at any time of the disease course; as such, CK and myoglobin levels should be carefully monitored.

Regarding the treatment of this condition, we have found no reports of complete response to corticosteroids in the absence of aggressive fluid therapy. Moreover, we wish to point out that lymphopenia, inflammatory parameters and lung infiltrates subsided after initiating methylprednisolone, lending support to corticosteroid benefit in COVID-19 treatment despite the absence of hypoxemia.

Some limitations in our report are the timing of muscle biopsy, which may have affected the results; genetic causes for rhabdomyolysis were not completely ruled out, and the simultaneous administration of hydroxychloroquine may be a confounding factor in attributing clinical improvement to corticosteroid use; nevertheless, the aforementioned drug carries less immunomodulatory properties and corticosteroids have been successfully employed in the treatment of several rhabdomyolysis cases, including those derived from non-viral etiologies, such as alcohol-induced rhabdomyolysis. [20]

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of Competing Interest

None.

Acknowledgements

We thank Tiago Marques, M.D. for helpful discussions, the Chiefs of Department of Internal Medicine II (Lurdes Alvoeiro, M. D.) and Infectious Diseases (Álvaro Pereira, M.D.) for support, Rafael Roque, M.D. of the Neurology Department for analysis of the muscle biopsy sample as well as all staff involved in the patient's treatment – all at the Santa Maria University Hospital. We also extend our thanks to Raquel Guiomar and her team at the National Health Institute Doutor Ricardo Jorge for performing SARS-CoV-2 RNA search *via* RT-PCR on the muscle biopsy sample.

References

[1] Adhikari S, Meng S, Wu Y, Mao Y, Ye R, Wang Q, Sun C, Sylvia S, Rozelle S, Raat H, Zhou H. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. Infect Dis Poverty 2020;9:29. . [online] Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7079521/.

[2] Ruan Q, Yang K, Wang W, Jiang L, Song J. Correction to: clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846–8. . [online] Available at: https://link.springer.com/article/10.1007%2Fs00134-020-05991-x.

[3] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18)1708–20 [online] Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2002032.

[4] Bosch X, Poch E, Grau J. Rhabdomyolysis and acute kidney injury. N Engl J Med 2009;361(1)62–72. . [online] Available at: https://pubmed.ncbi.nlm.nih.gov/19571284/.

[5] Fadila M, Wool K. Rhabdomyolysis secondary to influenza a infection: a case report and review of the literature. N Am J Med Sci 2015;7(3)122. . [online] Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4382767/.

[6] Chan J, Lau S, To K, Cheng V, Woo P, Yuen K. Middle east respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-Like disease. Clin Microbiol Rev 2015;28(2)465–522 [online] Available at: https://pubmed.ncbi.nlm.nih.gov/25810418/ [Accessed 21 June 2020].

[7] Chen L, Hsu C, Tian Y, Fang J. Rhabdomyolysis associated with acute renal failure in patients with severe acute respiratory syndrome. Int J Clin Pract 2005;59(10)1162–6. . [online] Available at: https://pubmed.ncbi.nlm.nih.gov/16178983/.

[8] Jin M, Tong Q. Rhabdomyolysis as potential late complication associated with COVID-19. Emerging Infect Dis 2020;26(7). . [online] Available at: https://pubmed.ncbi.nlm.nih.gov/32197060/.

[9] Suwanwongse K, Shabarek N. Rhabdomyolysis as a presentation of 2019 novel coronavirus disease. Cureus 2020;12(4)7561. . [online] Available at: https://www.cureus.com/articles/30228-rhabdomyolysis-as-a-presentation-of-2019-novel-coronavirus-disease.

[10] Singh U, Scheld W. Infectious etiologies of rhabdomyolysis: three case reports and review. Clin Infect Dis 1996;22(4)642–9. . [online] Available at: https://pubmed.ncbi.nlm.nih.gov/8729203/.

[11] Hirohama D, Shimizu T, Hashimura K, Yamaguchi M, Takamori M, Awatsu Y, Tsujino M, Mizutani T. Reversible respiratory failure due to rhabdomyolysis associated with cytomegalovirus infection. Intern Med 2008;47(19)1743–6. . [online] Available at: https://pubmed.ncbi.nlm.nih.gov/18827428/.

[12] Moore J, June C. Cytokine release syndrome in severe COVID-19. Science 2020;368(6490)473–4. . [online] Available at: https://science.sciencemag.org/content/368/6490/473.

[13] Russell C, Millar J, Baillie J. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395(10223)473–5. . [online] Available at: https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930317-2.

[14] Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet 2020;395(10225)683–4. . [online] Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30361-5/fulltext.

[15] Villar J, Confalonieri M, Pastores S, Meduri G. Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress Syndrome Caused by Coronavirus Disease 2019. Critical Care Explorations 2020;2(4)e0111. . [online]Available at: https://journals.lww.com/ccejournal/fulltext/2020/04000/rationale_for_prolonged_corticosteroid_treatment.18.aspx.

[16] The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. N Engl J Med 2020;1–11, doi:http://dx.doi.org/10.1056/nejmoa2021436.

[17] NIH. Coronavirus Disease. (COVID-19) treatment guidelines Available at: https://covid19treatmentguidelines.nih.gov/. Nih 2020;2019:130. 2019.

[18] Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: a systemic review and a Clinician's perspective. Diabetes Metab Syndr Clin Res Rev 2020;14:971–8, doi:http://dx.doi.org/10.1016/j.dsx.2020.06.054.

[19] Veronese N, Demurtas J, Yang L, Tonelli R, Barbagallo M, Lopalco P, Lagolio E, Celotto S, Pizzol D, Zou L, Tully M, Ilie P, Trott M, López-Sánchez G, Smith L. Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature. Front Med (Lausanne) 2020;7:170. . [online] Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7193030/.

[20] Antoon J, Chakraborti C. Corticosteroids in the treatment of alcohol-induced rhabdomyolysis. Mayo Clin Proc 2011;86(10)1005–7. . [online] Available at: https://pubmed.ncbi.nlm.nih.gov/21964178/.