

# Management of a case of COVID-19 with adrenal crisis at a semi-urban primary healthcare center

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### ABSTRACT

*Prolonged steroid use and the resultant adrenal insufficiency pose an increased risk of severe disease in patients with COVID-19. We describe here a case of Covid-19 with adrenal crisis in an elderly man at a semi-urban primary healthcare center. He and his family were forced to leave their home because of being infected with SARS-CoV-2. He was managed for adrenal crisis at a limited resource setting with a good outcome. This case also highlights the importance of social stigma related to COVID-19 in Bangladesh.*

**Key words:** COVID-19, SARS-CoV-2, adrenal insufficiency.

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### INTRODUCTION

Chronic glucocorticoid use is the most common cause of adrenal insufficiency (AI) and has been linked to increased risk of severe viral infections due to the immunosuppressive effects of glucocorticoids and associated AI.<sup>1-4</sup> An infective episode in such patients may lead to an adrenal crisis.<sup>5</sup> Here, we present a case of an adrenal crisis triggered by severe COVID-19, where an immediate induction of parenteral steroid in a resource-poor, rural health care set-up could save the patient.

### CASE REPORT

A 65-year-old man, with COVID-19, presented at the Corona Isolation Unit of Debidwar Upazila Health

Complex, Cumilla on 2nd May, 2020 with a 10-day history of high-grade fever and cough. He had breathlessness over the preceding two days. On initial assessment, the patient was found lethargic, febrile (temperature 103° F) and confused (GCS 11/15). He also had hypoxia (SpO<sub>2</sub> 86% at room air), hypoglycaemia (3.8 mmol/L), tachypnoea (respiratory rate 24/min) and hypotension (90/60 mmHg). There was no sign of meningeal irritation or hypercapnia.

Initially, he was diagnosed as a case of type 1 respiratory failure due to severe COVID-19 pneumonia, with hypoglycaemia and metabolic encephalopathy. In view of the clinical findings of hypotension, hypoglycaemia, lethargy and confusion, further enquiry revealed that the patient was on prednisolone and dexamethasone for the past two years which was prescribed by local village quack for musculoskeletal pain. Keeping in mind the history and physical findings the patient was clinically diagnosed as a case of adrenal crisis precipitated by SARS-CoV-2 infection. To confirm the diagnosis, a short ACTH stimulation test could had been done, but as patient was in shock and this facility was not available in UHC without further delay he was treated with intravenous hydrocortisone (100 mg stat followed by 100 mg 6 hourly), normal saline, supplemental oxygen,

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broad-spectrum parental antibiotics, enoxaparin (60 mg subcutaneously once daily), insulin and advised to lie in prone positioning. Overnight, the patient's condition improved dramatically. The next morning his blood pressure was 110/70 mmHg, random blood glucose and GCS became 5.8 mmol/L, 13/15 respectively. Oxygen requirements were decreased. Haematological and biochemical investigation showed low serum sodium and elevated CRP. Results of investigations are shown in Table I. Chest x-ray showed bilateral inflammatory lesions suggestive of COVID-19 (Figure 1). Ferritin, LDH, D Dimer, ABG could not be done at Debidwar.

**Table I** Laboratory parameters of patient with COVID-19 and adrenal insufficiency

Parameters	Normal value	Patients value (Day 1)
Complete blood count		
Total WBC count	4,000-11,000/ cumm	8800/ cumm
Haemoglobin	13-17g/dl	11.3g/dl
Neutrophil (%)	40-75%	72%
Lymphocyte	20-45%	21%
Monocyte	2-10%	4%
Eosinophil	1-6%	3%
Basophil	0-2%	0%
Platelet count	150,000-450,000/ cumm	2,30,000/ cumm
CRP	Upto 6U/L	24U/L
Serum electrolytes		
Serum Sodium	135-145mmol/L	118mmol/L
Serum Potassium	3.5-5.5mmol/L	3.8mmol/L
Serum chloride	96-106mmol/L	102 mmol/L
Serum HCO <sub>3</sub>	22-28mmol/L	24mmol/L
Serum Creatinine	0.7-1.2mg/dl	1.2mg/dl
SGPT	40U/L	42 U/L

He was observed closely and his conditions improved gradually over the subsequent 2 weeks. He could eat,



**Figure 1** X-Ray chest PA view: bilateral inflammatory lesions

use the restroom with minimal effort and overall he felt better. In the meantime, the dosage of hydrocortisone (50 mg 6 hourly) was adjusted and then replaced by oral hydrocortisone (initially at 200 mg daily and later on gradually tapered to physiological dose as per withdrawal protocol). The insulin dose was adjusted according to blood glucose levels. Serum sodium returned to normal. Enoxaparin was switched to rivaroxaban (10 mg daily for 1 month). After 2 weeks, his 2<sup>nd</sup> sample of RT-PCR for SARS-CoV-2 came back positive. He was advised to go home as his condition was stable. The patient refused to go home as the local people threatened him not to return home. Telemedicine team repeatedly tried to convince the village people but the community people persistently forbade him from returning to his village. Therefore, decision was taken to keep him in hospital isolation until his tests become negative. He was then discharged after five weeks when he tested negative (5<sup>th</sup> sample) for SARS-CoV-2.

The attending physicians had to bear the expenses of his medications and hospital stay as the patient was not solvent enough. Later the attending doctors came to know that the all the family members of the patient were forcibly driven out of the village along with the patient

when he was found positive for COVID-19. The helpless patient along with his wife and children, endured the five week ordeal at health center for being a COVID-19 case.

## DISCUSSION

Tertiary AI is the leading cause of AI in general population. In a retrospective study in the UK, 33% of patients taking various forms of steroids were found to have tertiary AI.<sup>4</sup> AI develops in patients on long-term steroid therapy. As a general rule, treatment with  $\leq 5$  mg of prednisolone per day for more than four weeks or treatment with  $\leq 20$  mg/day of prednisone for more than two weeks, especially if not given on a circadian basis, is associated with tertiary AI.<sup>6,7</sup>

Patients with AI have an increased risk of infection due to their ineffective innate immune response, which is characterized by increased monocytes and decreased cytotoxic NK cells with failure of IgG-mediated activation due to shedding of its surface receptor (CD16).<sup>8,9</sup> This can affect antiviral immune defence mechanisms and make patients more susceptible to viral respiratory tract infections.<sup>10,11</sup> The altered immune response can also contribute to worsening COVID-19 infection in severe acute respiratory distress syndrome (ARDS) due to an impaired first-line of defence.<sup>7</sup> The hypothalamic-pituitary-adrenal axis (HPA) plays a vital role in the stress-induced immune response and the lack of a physiological increase in glucocorticoid secretion in patients with AI during mild illness intuitively carries the risk of advancing to more critical stages, especially with inadequate replacement therapy. The whole scenario may further be complicated due to development of microthrombi and cortical necrosis in adrenals caused by SARS-CoV-2, which was observed in UK autopsy series of COVID 19 patients.<sup>12</sup> Glucocorticoids have both a stimulating and inhibitory effect on the immune response, depending on the timing and circulating levels.<sup>13</sup> In the early stages of infection, physiological glucocorticoid levels are required to strengthen the immune system, which, in turn, activates the HPA to increase the release of glucocorticoids from the adrenal glands and reach higher concentrations responsible for mild immunosuppression, which ultimately decrease autoimmunity and cytokine toxicity.<sup>7</sup> These physiological responses are lost in AI. Besides, COVID-19 pneumonia itself adversely affects the remaining

adrenal function and worsens the outcome by releasing cytokines.<sup>14</sup> Since adrenal crisis precipitated by infection is the leading cause of death in patients with AI, immediately at the onset of illness, the change in glucocorticoid regimen should be made as described in "Sick Days Rules" and should not wait for laboratory confirmation.<sup>15-18</sup> In patients with AI, who develop an acute infection with COVID-19, the dose of glucocorticoids should be doubled as soon as symptoms appear or an oral stress dose of 20 mg hydrocortisone should be given every 6 hours. Patients receiving 5 to 15 mg of prednisolone per day should take 10 mg of prednisolone every 12 hours. Patients with oral prednisolone  $>15$  mg should continue their usual dose, but be divided in to two equal amounts of at least 10 mg each.<sup>5</sup> Patients who are clinically deteriorating should start an immediate (self) injection of hydrocortisone 100 mg intramuscularly (intravenously in hospital), followed by hydrocortisone 50 mg intramuscularly (intravenously in hospital) every 6 hours or a continuous intravenous infusion of 200 mg of hydrocortisone every 24 hours. Afterwards, gradual reduction of the stress dose of hydrocortisone to the double of the usual replacement dose at discharge is recommended.<sup>5-7,19</sup>

The prompt initiation of the systemic steroid was the crux in the management of this patient. Initiation of systemic steroid corrected his AI and also alleviated the hyperinflammatory states of COVID-19. At the onset of epidemics, steroid use was prohibited due to its unfavourable experience in previous coronavirus outbreaks.<sup>20</sup> Later in the RECOVERY trial, the benefits of steroids in oxygen-dependent COVID-19 patients were established.<sup>21</sup> Recent meta-analysis further strengthened the conclusion of the RECOVERY trial.<sup>22,23</sup>

Treatment of hyponatremia was also of paramount importance in these particular cases, along with other interventions. Syndrome of inappropriate antidiuretic hormone secretion with hyponatremia is an established feature of COVID-19<sup>24</sup>; moreover, hyponatremia is also a common association of adrenal crisis.<sup>25</sup> With intravenous hydrocortisone and an infusion of normal saline, the patient's condition improved significantly overnight. Although within two weeks, the patient became asymptomatic, it required five weeks for his COVID-19 RT-PCR test to be negative. In critically ill

and immunocompromised patients, RT-PCR test for SARS-CoV-2 may remain positive for an extended period. However, consistently positive RT-PCR does not always reflect a virus capable of replication and is generally not infectious.<sup>26</sup>

The unique social circumstances surrounding this COVID-19 patient brings into light the importance of empathy and flexibility when dealing with patients in a particular social context. In this context, forced stay in the hospital for a longer duration of time incurred significant amount of medical expenses and psychological trauma to the patient and his family. This is an example of social conflict that may arise in an epidemic situation due to a contagious agent. Had the attending physician not been as generous, the outcome would possibly have been drastically different.

**Authors' contribution:** CSP was involved in patient management and manuscript writing. NC was involved in patient management. WMMH was involved in manuscript writing. All authors read and approved the final manuscript for submission.

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**Consent:** Taken from the patient for this publication.

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