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COMBINED HYPERGLYCEMIC EMERGENCIES (DKA AND HHS) WITH COVID-19 AT ADMISSION AT A COVID CARE CENTER- CASE SERIES

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ABSTRACT Diabetes as comorbidity is associated with increased mortality in patients with SARS CoV-2 infection. We report a case series of 05 cases of combined hyperglycemic emergencies (diabetic ketoacidosis (DKA) plus hyperosmolar hyperglycemic state (HHS)) from the COVID-19 care center observed for 02 months. The Mean Charlson comorbidity index was 3.2, mean APACHE score at presentation was 13.4, and mean SOFA at presentation was 5.2. All had ARDS with fatal outcomes was seen in 03 out of 05 cases. Serial rising titers of D-dimer and IL-6 were associated with a higher incidence of mortality. In this case series, we observed that the diabetic patients are at risk of developing uncontrolled Hyperglycemia associated with COVID-19 and difficult to manage hyperglycemic emergencies. The associated increase in inflammatory markers, e.g D- Dimer, IL-6 are linked to insulin resistance with poor glycemic control and outcome.

KEYWORDS :

INTRODUCTION

Diabetes is one of the most common comorbidities associated with COVID- 19 infection and it has a significant association with morbidity and mortality especially in patients admitted in the ICU setting. [1-4]

There are various pathophysiology associated with uncontrolled hyperglycemia in diabetic patients. It includes poor compliance to medication, effects of lockdown, associated raised inflammatory markers and cytokine storm leading to insulin resistance, increase in counter-regulatory hormones, altered angiotensin-converting enzyme 2 (ACE2) expression, late presentation to the hospital [3,5], in addition to damage of ACE2 receptors in the pancreatic islets leading to islet damage and acute diabetes[6]. Diabetes and the raised inflammatory markers like IL-6, promote ketogenesis, insulin resistance and precipitates diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), and uncontrolled hyperglycemia. [7]

Literature review revealed that there are only a few studies reporting both DKA and HHS as a combined complication of diabetes in COVID-19.[8, 9] But evidence are emerging. Here we present a case series of clinical and biochemical characteristics of 5 COVID-19 patients (observed for 02 months), with combined DKA and HHS, admitted in ICU of COVID care center, at Pune, India.

CASE SERIES

Demographic and patients characteristics at presentation in the emergency department are presented in Table 1. Three male and two females T2DM patients, with an age range of 53 to 75 years, are part of this case series. There were 03 males and 02 females amongst the cases. All patients had severe COVID-19 pneumonia and were on oral antihyperglycemic medication for Type II DM. The mean Charlson comorbidity Index was 3.2 for the cases. Mean APACHE II at admission and mean SOFA score at admission were 13.4 and 5.2 respectively. The mean Blood glucose was 474 mg/dl and HbA1C at admission was 7.8. Patients presented with chief complaints of fever, cough, dyspnea, and a positive report for SARS CoV-2.

Table1: Patients baseline characteristics and condition at presentation in emergency department

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5
AGE (years)	60	53	75	54	60
Sex	Female	Male	Male	Female	Male
Medical History	T2DM, HTN	T2DM, HTN	T2DM, HTN	T2DM, HTN	T2DM
SARS-CoV-2	Positive	Positive	Positive	Positive	Positive
Day of presentation at center post illness	Day 6	Day 4	Day 8	Day 5	Day 10
BPS/BPD (mm Hg)	170/102	144/84	168/88	108/84	140/100
HR (beats per minute)	100	110	100	130	120
RR (breaths per minute)	34	37	34	34	28
SpO_2 room air (%)	86	68	82	55	78
SpO_2 Non-rebreathing mask (%)	96	98	91	69	90
Ketone Bodies (Urine)	Positive	Positive	Positive	Negative	Negative
Random blood sugar (mg/dL)	424	526	480	412	528
HbA1c (%)	5.8	6.8	9.3	7.4	9.8
SOFA score	4	4	4	6	8
APACHE II score	10	10	12	17	18
D dimer (ng/ml)	1387	554	843	5005	2797
IL-6 (pg/ml)	21.6	151	865	395	247
CRP (mg/dL)	121	151	167	194	108
LDH (IU/L)	914	174	878	2023	973
Triglycerides (mg/dL)	67.4	324	143	138	234

SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; T2DM, Type 2 diabetes; HTN, Hypertension; BPS, Blood pressure systolic; BPD, Blood pressure diastolic; HR, Heart rate; RR, Respiratory rate; HbA1c, Hemoglobin A1C; SOFA, Sequential organ failure assessment; APACHE, Acute physiology and chronic health evaluation; IL-6, Interleukin-6; CRP, C-Reactive Protein; LDH, Lactate dehydrogenase.

At initial evaluation in the emergency department, all the patients were afebrile, cases 1,3, and 5 were conscious and oriented, however, cases 2 and 4 were drowsy, confused and agitated, at presentation. Electrolytes were within normal limits in all the patients. Urine and Blood cultures and serial procalcitonin were negative for bacterial infection. ECG showed sinus tachycardia and chest X-ray revealed diffuse bilateral ground-glass opacities corroborative of typical of COVID-19 (Fig1A to Fig 1E).

Figure 1: X-rays of DKA and HHS combined COVID positive cases at presentation in the covid-care center

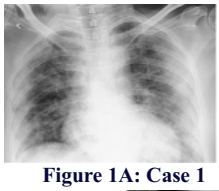

Figure 1A: Case 1

Figure 1B: Case 2

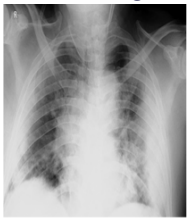

Figure 1C: Case 3

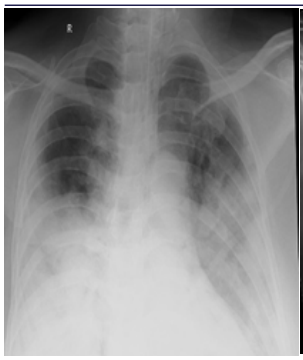

Figure 1D: Case 4

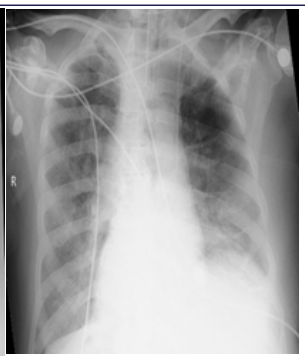

Figure 1E: Case 5

All five patients were treated as a case of severe COVID pneumonia with acute respiratory distress syndrome with DKA/HHS and managed with oxygen support through non-invasive ventilation, insulin infusion, broad-spectrum antibiotics, antihypertensives, balanced fluid resuscitation, anticoagulants, steroids, and antivirals (Remdesivir) as per institutional Protocol.

OUTCOMES

The mean hospital stay in over case series was 10.4-days. We observed that Serial D-dimer was a marker of prognosis in these patients. Rising D-dimer was associated with poor outcomes in the patients. Complications seen were acute kidney injury (AKI), hepatitis, and sepsis. In 02 patients with the favorable outcome, the acidosis resolved in 03 days while in 03 fatal cases the acidosis never settled during the entire length of hospital stay.

In case 1 and 3 DKA resolved and respiratory status improved. Serial inflammatory markers were showing an improving trend, D-dimer declined from 1387 ng/ml to 245 ng/ml and from 843 ng/ml to 688 ng/ml, in cases 1 and 3, respectively. There was a clinical, biochemical, and microbiological resolution of the symptoms, and patients were discharged from the hospital on Day 16 and 12, respectively.

However, the condition of cases 2, 4, and 5 continued to worsen. Case 2 was put on invasive mechanical ventilation on Day 2 of hospitalization. Serial inflammatory markers showed a worsening trend (D-dimer 554 ng/ml to 7839 ng/ml), the condition was further complicated by multiple organ dysfunction syndromes (MODS) requiring vasopressor support. Antimicrobials were also upgraded. However, the patient succumbed to his illness on Day 6 of Hospitalization. Case 4 was intubated on Day 3 of illness, serial D-dimer showed worsening trend 5005 ng/ml to 10150 mg/ml, stay was further complicated by AKI and patient succumbed to her illness on Day 10 of the hospitalization. Condition of case 5 worsened with serial D-dimer worsening from 2797 ng/ml to 4938 ng/ml. The patient was put on intermittent mandatory ventilation on Day 4 of hospitalization, which was further complicated by Sepsis with MODS, AKI, and Atrial fibrillation, which were managed conservatively. Despite all effort's patient succumbed to his illness on Day 10 of the hospitalization.

DISCUSSIONS

Hyperglycemic emergencies are on a rising trend in the setting of the current COVID -19 pandemic. There are various factors associated with this which include poor compliance and lockdown related poor adherence to dietary modifications, exercise, and antidiabetic medications, cytokine storm and insulin resistance, [7] monitoring Issues in a pandemic situation, and delayed presentation to the hospital. Secondary diabetes is also increasing owing to the glucocorticoid therapy related to the treatment of COVID-19 with ARDS. As we Know glucocorticoid therapy and Remdesivir treatment also increase insulin resistance and further worsening glycemic control. [4,10] The COVID-19 is also known to worsen glycemic control by various mechanisms including inhibition of the ACE receptors. [3] In our practice, we suspect DKA more often than considering Combined DKA/HHS. As one of the systemic reviews reports 17% of the patients had combined DKA/HHS. This could be an underestimation as very few studies had reported effective serum osmolality. Clinical suspicion of both emergencies presenting together is different as the patients with combined DKA/HHS tend to be more volume-depleted and hence require more intravenous fluids in the first 24 h.[9] Hence early differentiation of DKA/HHS from isolated DKA is essential for management, especially in the COVID-19 pandemic. Here in our case series, all patients had T2DM which may be due to the higher prevalence of T2DM in society.

The management of DKA/HHS includes adequate fluid resuscitation, insulin replacement, potassium supplementation[11,12], and correction of the precipitating cause. Profound dehydration is the norm in such patients and fluids are the cornerstone of therapy. In adults with DKA, the American Diabetes Association and the UK guidelines recommend the aggressive use of isotonic saline during the first 24 h.[12,13] However, in a patient with COVID-19, there are concerns about precipitating ARDS with aggressive fluid resuscitation. [14] Hence, there is a dilemma in fluid management in such cases. The UK guidelines recommend conservative use of isotonic saline in COVID-19 patients with DKA. After the initial fluid bolus, the subsequent use of fluid must be guided by the patient's weight and the pH at presentation. Patients with a pH 7.1 would benefit from a more aggressive fluid replacement regimen than those with lesser degrees of acidosis. [15] There is only one case series with conservative fluid replacement reported in 12 patients in only one series [9] and other few studies [16,17]. In Our case series also, we used a conservative fluid replacement approach. In all our cases intravenous insulin infusion was used with Slightly higher insulin requirement and longer duration for resolution of Acidosis. Electrolytes management also remains an important part of the treatment.

SARS CoV-2 binds to ACE2 with subsequent downregulation of the enzyme and reduced degradation of aldosterone, leading to hypokalemia. [18] So patients with COVID-19 are at increased risk of hypokalemia[19]; hence, hypokalemia can be expected to be all the more profound in COVID-19 patients with DKA/HHS. So, it is very important to monitor serum potassium and replenish it accordingly.

An important complication of DKA and COVID-19 includes the development of a hypercoagulable state with an increased risk of thrombotic events [11] hence patients managed with anticoagulant therapy. By this case series, we present the commonly missed combined hyperglycemic emergencies and emphasize suspicion, early detection, evaluation, and the practice of calculation of the serum osmolality in a patient with diabetes with COVID-19. It may be difficult to control the blood sugar levels in presence of ongoing raised inflammation as in the case of COVID-19. Fluid management remains the grey area and definitive study and recommendations are required in these patients with combined hyperglycemic emergencies. The optimal dose and duration of the glucocorticoid also remain the challenge in such cases. We also noticed in our case series that serial D-dimer may have a role in prognostication in COVID-19 patients with T2DM.

CONCLUSIONS

Combined DKA/HHS is a less frequently reported diagnosis in COVID-19 patients with pre-existing diabetes mellitus. Hence in this case series, we emphasize the clinical suspicion, early diagnosis, measurement of effective serum osmolality is essential in the management of such patients. Fluid resuscitation, dose, and duration of steroids, an association of inflammatory markers with glycemic control remain the scope for future prospective studies in case of severe COVID-19 pneumonia with ARDS.

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