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Diabetic Ketoacidosis and New Onset Diabetes Mellitus Precipitated by COVID-19 Infection

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Abstract

Background: Diabetes Mellitus have been reported frequently in patients with the new corona virus disease- 2019, COVID- 19. It has been associated with progressive course and worse outcome. Recently, case reports and small cross-sectional studies described diabetic patients who develop diabetic ketoacidosis (DKA) when infected with COVID -19. The incidence of DKA has been found to be high in patients with type 1 (T1DM) and type 2 diabetes Mellitus (T2DM) admitted to hospital with COVID-19.

Case presentation: We present a 47-year-old patient who was not known to have DM but presented with generalized body aches, fatigue and nocturia 4 days prior to admission. His lab results showed high blood glucose, high anion gap metabolic acidosis and ketonuria diagnostic of DKA. He also tested positive for COVID-19 and his Chest X-Ray was consistent with Covid 19 Pneumonia. He was successfully managed with Intravenous fluids and Insulin as per DKA protocol. He required intravenous antibiotics, steroids and high flow oxygen for COVID 19 pneumonia. He was discharged after 16 days in stable condition.

Conclusion: COVID-19 infection can be complicated by DKA and development of DM in previously non-diabetic individuals. Very few cases have been reported in the literature on COVID-19 infection precipitating DKA in a newly diagnosed patient of diabetes mellitus type II.

Keywords: DKA; COVID-19; ACE2; T2DM

Abbreviation: DKA: Diabetic Ketoacidosis; DM: Diabetes Mellitus; T1DM: Diabetes Mellitus Type 1; T2DM: Diabetes Mellitus Type 2; ACE2: Angiotensin-Converting Enzyme 2; SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus-2; COVID-19: Corona Virus -19; ICU: Intensive Care Unit; CRP: C-Reactive Protein; LDH: Lactate Dehydrogenase; Na: Sodium; Cl: Chloride; K: Potassium; BUN: Blood Urea Nitrogen; Hgb: hemoglobin; ECG: Electrocardiogram; ED: Emergency Department

Introduction

During COVID-19 pandemic, patients with previous history or underlying cardiovascular condition were at higher risk for developing severe symptoms and poor prognosis. Diabetes Mellitus in particular, was found to be a risk factor for severe disease [1]. A history of diabetes was associated with 22.5% of COVID-19 ICU admissions in one case series [2] and a mortality rate up to 16% among people with diabetes and without other comorbidities [3]. The development of DKA can in itself add to this high mortality in COVID -19 patients, Recent studies have demonstrated that COVID-19 can utilize angiotensin-converting enzyme 2 (ACE2) on the surfaces of epithelial cells to bind and gain entry to infected cells [4,5]. Similar findings were reported during SARS outbreak in 2006 [6]. Binding of ACE2 by SARS-CoV-2 in COVID-19 may play an important in the pathogenesis of the disease on one hand and could predispose patients to hyperglycemia and development of DM on the other hand. Herein, we describe a patient who was previously healthy, but presented with DKA and new onset of DM complicating COVID-19 pneumonia.

Case Presentation

A 47 years old, gentleman, medically free has presented to the emergency department (ED) with fatigue and decrease in activity for 4 days along with generalized body aches and nocturia (about 6-7 times/day). He went to a private health-care centre, where his blood sugar was measured and was 15.5mmol/l.

He denied any respiratory symptoms or chest pain. He had no history of fever, headache, nausea, vomiting, diarrhea, abdominal pain or burning sensation on micturition, he works as a driver. Other than he used to go to grocery shops in the past weeks frequently, there was no clear contact history with confirmed (COVID-19) cases, He is non-smoker and has no family history of DM.

Upon examination in the emergency room, he was conscious and oriented to time, place and person but looked dehydrated, he was afebrile, his respiratory rate was fluctuating 26-33/min, he had resting tachycardia 108/minute and O_2 saturation was 94% on 2L nasal cannula, he did not display Kussmaul's breathing.

His body mass index was 26.3kg/m^2 with no signs of insulin resistance.

laboratory investigations were significant for hyperglycaemia 19.9mmol/L high anion gap metabolic acidosis: 26, *p*H 7.2 and ketonuria +4, confirming the diagnosis of DKA.

The rest of his investigations showed the following:

a) BUN: 4.7mmol/L, normal range (2.5-6.4).

b) Creatinine: 106mcmol/L, normal range (62-115).

c) Na: 134mmol/l, normal range (135-145).

d) K: 4.7mmol/l, normal range (3.5-5.1).

e) Cl: 93mmol/l, normal range (98-107).

f) S. lactate: 1.2mmol/l normal range (0.5-1.1).

g) WBC: 5.730 x 10^9/L, normal range (4-11).

h) Lymphocytes: 0.20 x 10^9/L.

i) Hgb: 166gm/L, normal range (130-180).

j) platelets: 177.9 x 10^9/L, normal range (140-450).

k) Chest x-ray: showed bilateral infiltration.

l) Insulin 14.9mIU/L, normal range (2.6-37.6mIU/L).

m) C-peptide 0.5(nmol/L), normal range (0.16-1.68nmol/L).

n) HbA1C: 6.2 %.

Oronasal swab was positive for Covid-19 by real-time reverse transcription-polymerase chain reaction (rRT -PCR) test (this is used with Roche MagNA Pure-96 (MP96) using MagNA Pure 96 DNA and Viral NA Small Volume Kit and Applied Biosystems QuantStudio7 Flex (QS7).

Inflammatory markers:

a) D dimer: 0.60mcg/ml, normal range (0.22-0.45).

b) LDH: 193unit/L, normal range (87-241).

c) Ferritin: 1694.2mcg/L, normal range (30-400).

d) CRP: 124mg/L, normal range (< 10mg/l Negative, >10mg/l Positive).

e) ECG normal sinus rhythm.

f) Cardiac enzymes and troponin were normal.

In ED, he received 10 units IV Insulin as a bolus and 1.5 litres of IV Normal saline and started on DKA protocol with insulin infusion, IV fluids and potassium replacements. Serum electrolytes were closely monitored. DKA resolved after 16hrs and he was transitioned to subcutaneous insulin therapy. He stayed in the hospital for 16 days and completed one week of antibiotics, azithromycin and ceftriaxone. Rapid response team was called to assess him after 3 days of admission due to desaturation. He was managed with 12 litres high flow oxygen and 6days course of methyl prednisolone 30mg three times daily. Eleven days later he was weaned off Oxygen, and he was discharged on Gliclazide 30mg once daily, Linagliptin 5mg once daily and Metformin 1gm twice daily. He was given follow up with diabetic clinic after one month.

Discussion

The patient in this case report was not known to be diabetic but presented with two life threatening conditions, DKA and COVID 19 pneumonia. The prompt recognition and management of these conditions resulted in good outcome.

Diabetic ketoacidosis (DKA) is a known complication of T1DM and less commonly in T2DM. It is usually triggered by acute stress including most commonly infection, but also acute myocardial infarction, stroke, and the new class of antidiabetic medication, sodium-glucose co-transporter-2 (SGLT-2) inhibitors [7,8].

The patient in this case report presented with DKA and newly diagnosed type 2 DM triggered by COVID 19 pneumonia. The underlying pathophysiology of glucose intolerance and its severe form DKA in Patients with COVID 19 is still not well understood.

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), responsible for COVID-19, uses ACE2 receptor to bind and enter to infected cells as a viral complex [5]. ACE2 is located in many organs including the heart, kidney, lung, and intestinal tissues where it converts angiotensin II to angiotensin 1. The clinical manifestations of SARS can be explained by the expression of ACE2 in various organs. In the pancreas, it was found that ACE2 is expressed in the endocrine part of the pancreas. This suggests that SARS coronavirus enters islets cells using ACE2 as its receptor and damages B-cell islets leading to insulin deficiency and development of acute diabetes [6]. This is supported by the findings of strong immunopositivity for ACE2 in pancreatic islets while exocrine tissues were only weakly positive [9]. Similarly, evidence in diabetic mice demonstrated that ACE2 activity levels were enhanced in the pancreas [9,10].

In addition to the direct B cell injury, the expression of ACE2 on the surface of the pancreas is downregulated following endocytosis of the virus-ACE2 receptor complex This in turn

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can lead to increase concentration of angiotensin II and inhibit insulin secretion [3,11]. These interactions between SARS-CoV-2 and the renin-angiotensin-aldosterone system (RAAS) might explain the underlying mechanism and pathophysiology of DKA. These 2 factors might have contributed to the acute worsening of pancreatic beta cell function and precipitated DKA in this patient. Whether these changes are transient or permanent remains to be investigated.

The presentation of the patient in this case report is consistent with the hypothesis that COVID-19, not only causes hyperglycaemia and insulin resistance in patients known to be diabetic [3,12], but can also predisposes newly diagnosed T2DM to DKA which can sometimes be resistant to treatment [13-15].

The development of diabetes and DKA can further complicate the course of COVID -19 infection. Diabetic patients with COVID -19 have worse prognosis than nondiabetics [1,3]. This could be explained in part by high inflammatory and pro-coagulant state in diabetics including IL-6, C-reactive protein, serum ferritin, coagulation index, and D-dimer [1,3,16].

Conclusion

In conclusion, infection with COVID- 19 can lead to uncontrolled hyperglycaemia, development of diabetes mellitus and DKA which can further complicate the course and outcome of COVID-19 infection. It is important to be aware of the possibility of DKA and acute diabetes in patients with COVID-19 who present with nonspecific symptoms. Further studies are needed to reveal the exact underlying pathophysiological mechanism of this serious condition.

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