Title: Successful management of COVID-19 mediated extensive bilateral pulmonary embolisms complicated by right ventricular strain and DKA – A Case Report

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KEY WORDS:

- Diabetic keto-acidosis
- acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19)
- Pulmonary embolism
- Right Ventricular (RV) strain

ABSTRACT:

COVID-19 can precipitate diabetic ketoacidosis (DKA) in patients with or without pre-existing diabetes. Similarly, the link between COVID-19 and thrombotic complications has been well established. Currently, no data addresses the management of patients with both extensive thromboembolic complications and DKA. We report a unique case on the successful clinical management of a 42-year-old male who presented with COVID-19 mediated extensive bilateral pulmonary embolisms complicated by right ventricular strain and DKA. The findings of the case suggest that pulmonary embolism and DKA management should follow current guidelines, except for using high fluid maintenance rates recommended in DKA treatment as fluid overload can be detrimental for the management of pulmonary embolism with right ventricular strain. We recommend that in patients presenting with these two COVID-19 related complications, simultaneously, treatment and progression prevention of their thromboembolic complications should take precedence over a goal directed DKA management.

INTRODUCTION:

The bidirectional relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) and severe metabolic complications from diabetes mellitus has been recognized in the literature.[1] Pre-existing diabetes mellitus is maintained to be one of the high-risk factors for developing COVID-19 and related complications. However, COVID-19 can also precipitate diabetic ketoacidosis (DKA) in patients with or without pre-existing diabetes.[1,2] Similarly, the link between COVID-19 and thrombotic complications has been well established, with an incidence of 20.0- 31%.[3,4]

Currently, no data addresses the management of patients with both extensive thromboembolic complications and DKA. This raises an important clinical conundrum, as management of DKA with aggressive fluid resuscitation carries the physiologic potential of exacerbating ventricular interdependence in patients who also suffer from COVID-19 mediated thromboembolic complications. We report a unique case on the successful clinical management of a 42-year-old male who presented with COVID-19 mediated extensive bilateral pulmonary embolisms complicated by right ventricular (RV) strain and DKA.

CASE REPORT:

42-year-old male with a medical history significant for unspecified psychiatric disorder, and recently diagnosed noninsulin dependent type 2 diabetes mellitus (NIDDM2) presented to the emergency department (ED) complaining of shortness of breath associated with subjective weakness, lethargy, and worsening nonproductive cough of 2-weeks' duration. On review of systems, he denied any anosmia, ageusia or changes in bowel habits. On arrival, the patient was hypoxic with oxygen saturations (SpO2) of 86-88% on room air, tachycardic with a heart rate (HR) of 120 and tachypneic with respiratory rates (RR) of 40s-50s. He was afebrile and normotensive.

Complete blood count (CBC) was significant for lymphopenic leukocytosis with neutrophilic predominance. Arterial blood gas was significant for compensated metabolic acidosis (Table 1). In-house-PCR test was positive for COVID-19. Testing for influenza A and B, parainfluenza viruses (1-4), adenovirus, Human metapnuemovirus, H. Rhinovirus-Enterovirus, Respiratory Syncytial Virus A and B, and mycoplasma pneumonia were all negative. Chest X-ray showed patchy infiltrates in the left mid and lower lobes consistent with viral pneumonia (Figure1A). Hemoglobin A1C was markedly elevated (Table1). Comprehensive metabolic panel and urine-analysis were consistent with anion gap metabolic acidosis in the setting of DKA and lactic acidosis (Table 1). Standard DKA management was initiated on arrival to the ED, with aggressive (4Liters of Lactated Ringers) intravenous fluid (IVF) resuscitation and insulin drip. He was started on empiric treatment for community acquired pneumonia (CAP) with a 5-day course of IV ceftriaxone and azithromycin due to a high index of suspicion of superimposed bacterial pneumonia in lieu of the unilateral chest x-ray findings. Electrocardiogram (EKG) showed sinus tachycardia, T-Wave inversion and q-wave in lead III, and an elevated ST segment elevation on aVR, consistent with right heart strain. A markedly elevated troponin was concerning for acute myocardial injury (Table 1). Computed Tomography Angiography (CTA) was obtained and showed extensive bilateral pulmonary embolisms, evidence of right ventricular strain (RV/LV ratio of 1.8), multifocal bilateral ground glass opacities in a peripheral distribution, and areas of wedge-like consolidation concerning for evolving infarction (Figure 1B-E). Transthoracic echocardiogram (TTE) was significant for RV strain. Bilateral venous duplex ultrasound was negative for deep venous thrombosis (DVT). The patient's calculated pulmonary embolism severity index (PESI) score of 112, and simplified PESI score of 2 placed

him at a class IV of 4.0-11.4%, 30-day mortality risk. Based on the patient's hemodynamic stability, grade IV PESI score, RV dysfunction and elevated cardiac troponins, bilateral pulmonary embolisms were graded as intermediate-high risk for an in hospital vs. 30-day mortality event.

The patient was transferred to the intensive care unit (ICU) for management of acute hypoxic respiratory failure and was placed on 100% fraction of inspired oxygen by high-flow nasal cannula. He did not require endotracheal intubation throughout his hospital course. The maintenance IV fluid rate was decreased to 75 mL/hour due to the risk of ventricular interdependence in the setting of right heart strain, and the patient's DKA was managed via insulin drip. On hospital day 2, IV fluids were discontinued following closure of anion gap. The patient then received systemic alteplase (tPA) infusion for thrombolysis of bilateral PE with significant improvement in respiratory status and resolution of tachycardia. The patient was transitioned to full-dose enoxaparin post-thrombolysis, with eventual initiation of direct oral anticoagulation with apixaban prior to discharge. Additionally, the patient was found to have low C-peptide concentration and negative autoantibodies to Islet cell -2 (IA-2) and glutamic acid decarboxylase antibody (GAD-Ab).

DISCUSSION:

In summary, we present the unique case of 42-year-old male who presented with conflicting COVID-19 related complications in the form of concomitant extensive bilateral pulmonary embolisms and DKA.

To our knowledge only one other case report exists addressing the clinical management of a patient afflicted by both of these COVID-19 mediated complications during the same hospitalization. Haider et al. described the successful management of a 46-year-old unvaccinated female who suffered from DKA and multiple sub-segmental pulmonary emboli despite receiving prophylactic anticoagulation.[5] However, the onset of her complications occurred in a successive fashion. This patient had DKA on initial presentation and by the time she developed pulmonary embolisms on hospital day 3, she had already received standard treatment and had achieved complete resolution of her DKA. In contrast, our patient presented to the ED with both afflictions, occurring simultaneously, posing a unique challenge to our team and forcing us to

think beyond standard methods of DKA management, in lieu of ventricular interdependence secondary to RV strain.

Although the exact mechanism of DKA in COVID-19 is not fully understood, it is believed that the viral entry into pancreatic islet cells may cause decreased insulin secretion by directly aggravating beta cell injury, and via downregulation of ACE-2 leading to unopposed angiotensin II, which may impede insulin secretion via activation of NF-κB and IL-6 pathways. [6-8] Thus, it can be easily inferred that COVID-19 does not cause type 1 diabetes per say, instead it injures pancreatic cells leading to an acute hypo-insulinomic period which precipitates DKA. Interestingly, this pattern of injury was supported by our case report, as our patient had low c-peptide levels but normal autoantibody to Islet cell -2 (IA-2) and glutamic acid decarboxylase antibody (GAD-Ab). Of note, our patient had a history of uncontrolled type II diabetes mellitus with a markedly elevated hemoglobin A1C (14.7), in conjunction with a suspected superimposed bacterial pneumonia infection. However, the incidence of DKA in adult type 2 diabetics is less than 2 cases in 1000 patient-years, making COVI-19 mediated DKA the likely culprit.[9,10]

It is unclear if the patient's psychiatric condition played any role on the development of DKA. Both the patient and his family were uncertain of the exact diagnosis and medication regimen the patient was receiving. At the time of admission, the patient reported receiving a monthly injection at an otherwise unspecified county hospital. Long acting injectable (LAI) antipsychotics include a subset of first- and second-generation antipsychotics (SGAs), and they are indicated in the treatment of schizophrenic patients suffering from unstable illness, chaotic social structure, and substance use disorder in the setting of oral medication non-adherence. Second generation antipsychotics are reputable for their high risk of metabolic disturbances, including hyperglycemia. Studies have demonstrated that the incidence of DKA in schizophrenic patient on SGAs is 10-fold higher compared to the general population; while the subset of patients already suffering from pre-existing diabetes mellitus have a 30-fold increased risk of DKA.[11,12] It is unclear whether the patient was taking a LAI-SGA. To our knowledge, there are no studies addressing risk difference of precipitating DKA in LAI-SGAs compared their oral counterparts. Nonetheless, it important to note that this is a weakness in our report, as the potential concomitant use of an LAI-SGA during the acute phase of the COVID-19 viral illness could represent a major confounding precipitating factor of DKA in this patient.

Management of DKA in COVID-19 patients is no different than in the non-COVID population. Although DKA protocols vary among institutions, the mainstay treatment involves aggressive intravenous fluid resuscitation (IVF), insulin administration and electrolyte repletion. The only difference lies in the use of subcutaneous insulin protocols rather than intravenous insulin infusions, owing to the need to limit frequency of contact of staff with infected patients. Fluid loss averages approximately 6–9 L in DKA. For this reason, the recommendation is to replace the total volume loss within 24–36 hours with 50% of resuscitation fluid being administered during the first 8–12 hours.[13] Thereafter, safe practice of fluid resuscitation in DKA is followed by hypotonic saline solution (0.45% saline) at a rate of 4–14 mL/kg/h as long as the patient is hemodynamically stable and corrected serum sodium is normal to high.[13] If a patient becomes hyponatremic based on corrected serum sodium, initiation of 0.9% saline at a rate of 150–250 mL/h is recommended until eunatremia is achieved.[14] In our case, the patient received aggressive the initial recommended IVF resuscitation, but implementation of the subsequent standard DKA protocol was limited by CTA findings, and instead he placed on low fluid resuscitation at 75mL/h, with successful gap closure.

Comparably to DKA, there are no high-quality clinical trials supporting interventions that go beyond standard indications of antithrombotic therapy in COVID-19 patients. As with traditional patients, prophylactic dosing with low-weight molecular heparin is preferred over higher dosing in most inpatients, including those in the ICU. Moreover, therapeutic anticoagulation is only initiated in patients with either documented or high clinical suspicion of venous thromboembolism (VTE). While the precise pathogenesis remains unknown, multiple etiologies have been proposed. It is hypothesized that the viral attachment to angiotensin-converting enzyme 2 (ACE-2) receptors in pulmonary epithelium and endothelium, leads to pro-inflammatory cytokine activation. This further activates the coagulation system via molecules such as interleukin 6, a prominent inducer of tissue factor which promotes thrombin generation.[15]

Acute right ventricular failure with resulting low systemic output is the leading cause of death in patient with high-risk PE.[16] Current guidelines for the management of acute pulmonary embolism recommend volume optimization but with caution in volume loading as over distending the RV can worsen ventricular interdependence and reduce the cardiac output.[17,18] In our case, patient already had received volume loading due to his presenting DKA, and upon further assessment of her volume status, additional fluid challenge could have resulted in

worsening of RV function. Therefore, the decision to run maintenance at a lower rate of the recommended based on her body weight. We did not have to use vasopressors, inotropes or mechanical circulatory support for this patient. Regarding anticoagulation, guidelines recommend LMWH and fondaparinux over unfractionated heparin (UFH) as they carry a lower risk of inducting major bleeding and heparin induced thrombocytopenia, hence the decision to use enoxaparin initially.[17,18] However, then he was switched to UFH due to the possibility of hemodynamic decompensation and need for primary reperfusion. Thrombolytic therapy has been associated with a significant reduction in the risk of hemodynamic decompensation.[19] Patient was provided with tPA on day 2 of his hospitalization with great results and marked improvement shortly after leading to his discharge on hospital day 8.

CONCLUSION:

The findings of the case suggest that running IV maintenance fluids at a lower rate of the recommended based on her body weight in DKA, may be key in the successful recovery of COVID-19 also suffering from concomitant extensive thromboembolism with RV strain. We recommend that in patients presenting with these two COVID-19 related complications, simultaneously, treatment and progression prevention of their thromboembolic complications should take precedence over a goal directed DKA management.

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Table 1. Laboratory Data

Variable	Reference Range, adults φ	Hospital Day 0	Hospital Day 2	Hospital Day 4	Hospital Day 8
Complete Blood Count (CBC)					
Leukocyte count (per μL)	4.5 - 11.0	15.4 **H**	13.2 **H**	7.7	10.4
Hemoglobin (g/dL)	14.0 - 18.0	18.2 **H**	15.7	14.1	12.6 **L**
Hematocrit (%)	42.0 - 52.0	56.5 **H**	46.3	42.1	38.7 **L**
Platelet (per μL)	150 - 400	324	300	280	290
Differential count (% per μL)					
Neutrophils	36.0-66.0	74.1 **H**	83.7 **H**	63.5	--
Lymphocytes*	24.0- 44.0	12.2 **L**	6.9 **L**	23.5 **L**	--
Monocytes	2.0- 8.0	10.5 **H**	7.1	5.9	--
Eosinophils	0.0- 5.0	0.0	0.0	0.0	--
Basophils	0.0- 1.0	0.1	0.5	0.3	--
Complete Metabolic Panel (CMP)					
BUN, serum (mg/dL)	8- 26	19	10	23	21
Creatinine (mg/dL)	0.61- 1.24	1.36 **H**	0.68	0.78	0.65
Glucose, serum (mg/dL)	65- 100	428 **H**	158 **H**	252 **H**	202 **H**
Sodium (mmol/liter)	136- 145	143	142	140	140
Potassium (mmol/liter)	3.5- 5.1	4.2	3.8	3.7	4.0
Chloride (mmol/liter)	101- 111	102	109	102	99 **L**
Carbon dioxide (mmol/liter)	21- 32	14 **L**	21	28	30
BUN/Cret	10-20	14	15	29	32
Anion gap (mmol/liter)	8-16	31 **H**	16	14	15
Total Bilirubin (mg/dL)	0.3- 1.2	1.4 **H**	1.2		
Lactic dehydrogenase (LDH) (U/L)	98- 192	--	360 **H**		
Alkaline phosphatase (U/L)	38- 126	103	69		
ALT (U/L)*	17- 63	20	17		
AST (U/L)*	15- 41	27	26		
Other values					
Beta-hydroxybutyrate (mmol/liter)	0.0- 0.26	6.30 **H**	--	--	--
C-reactive Protein (mg/dL)*	1.0- 0.748	6.989 **H**	10.745 **H**		
Lactic Acid (mmol/liter)	0.5- 2.2	4.2 **CH**	2.7 **H**		
Troponin (pg/mL)	0.0- 19.7	928.9 **CH**	763.1 **CH**		
BNP (pg/mL)	0.0- 100	--	541 **H**		
Ferritin (ng/mL)*	23.9- 336.2	--	718.7 **H**	579.3 **H**	--
Partial Prothrombin time (sec)	23.8- 36.4	24.0	>150.0 **CH**	41.0 **H**	--
Fibrinogen (mg/dL)*	221- 525	--	513	414	--
D-dimer (μL/mL)*	0.0- 0.55	--	3.48 **H**	1.58 **H**	--
Interleukin 6 (pg/mL)*	<= 2.0		6.0 **H**		
Serum C-peptide	0.8- 3.5	--	0.4 **L**	--	
Autoantibody to Islet Cell -2 (IA-2) (U/mL)	0.0- 7.4		<5.4		
Glutamic Acid Decarboxylase Antibody (U/mL)	0.0- 5.0		<5.0		
Hemoglobin A1C (%)	4- 5.6	14.7 **CH**	--	--	
Arterial Blood Gas					
pH	7.35-7.45	7.1 **CL**	--	7.42	--
PaCO2 (mmHg)	35.0- 45.0	25 **L**	--	33**L**	--
PaO2 (mmHg)	70- 100	105 **H**	--	90	--
Urine					
Glucose	negative	3+ **H**			
Ketones	negative	2+ **H**			
protein	negative	2+ **H**			
White blood cells (per high-power field)	0-2	1			
Red blood cells (per high-power field)	0-2	2			

-- = denotes not available. **L** denotes low levels, **CL** denotes critically low levels, **H** denotes high levels, and **CH** denotes critically high levels.
φ Reference values are affected by many variables not limited to patient population and laboratory methods used. The ranges used at Bethesda East Hospital are for non-pregnant adults and those who do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.
*Evidence-based laboratory findings among hospitalized patients with COVID-19.

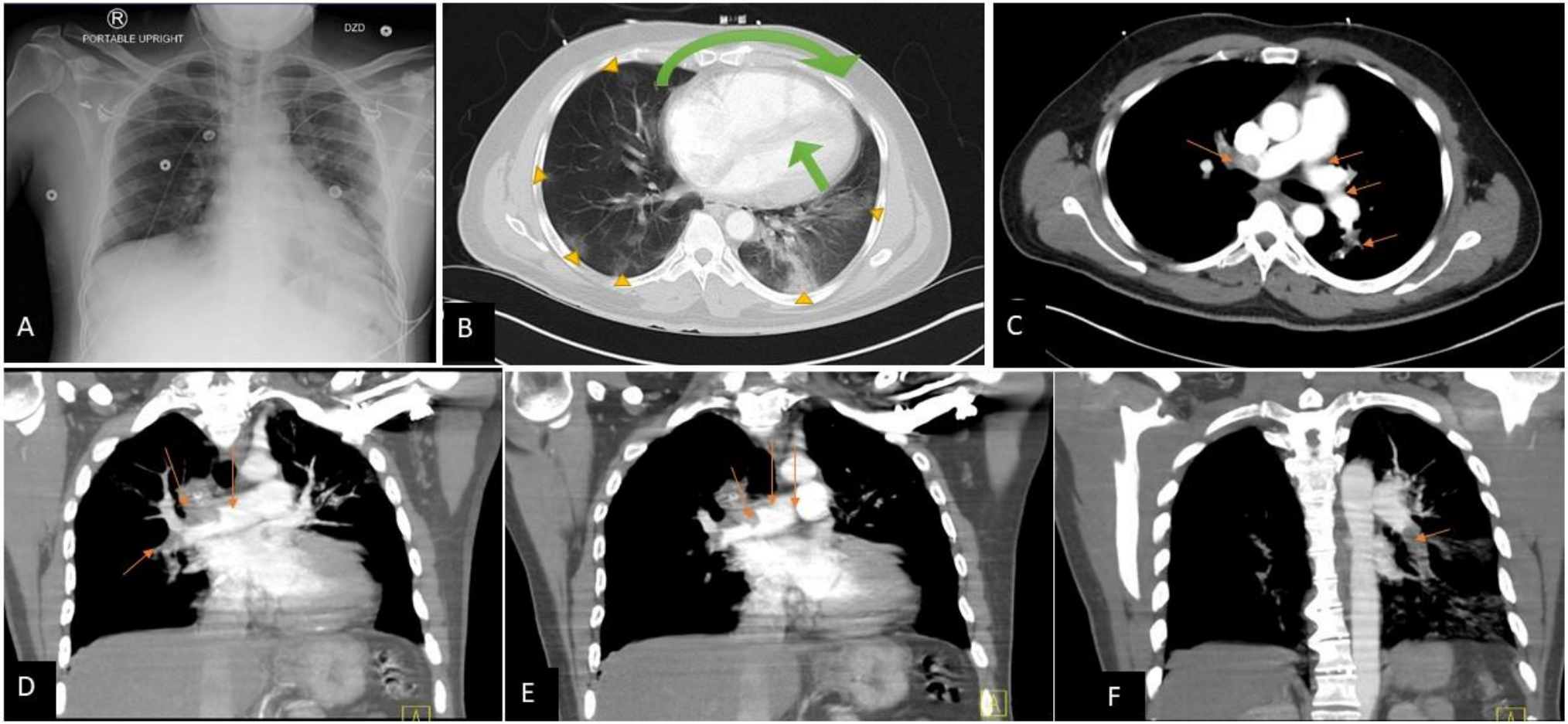

Figure 1. Anterior Posterior (AP) chest radiograph and coronal and axial computed tomography angiography (CTA). Panel A shows portable upright chest radiograph obtained on admission showing patchy multifocal infiltrates in the left mid and lower lung consistent with viral pneumonia and right internal jugular catheter noted with the distal tip in the right atrium. Panel B (yellow triangles) shows bilateral peripheral ground-glass opacities on lung window. Green arrows denote clockwise rotation, bowing (P-sign) and flattening of the interventricular septum, consistent with right heart strain. The RV/LV ratio is approximately 1.8 Panels C-F shows axial and coronal CTAs with orange arrows denoting bilateral pulmonary embolisms.