Successful Treatment of Pulmonary Embolus Secondary to Diabetic Ketoacidosis with Tissue Plasminogen Activator

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Authors' contributions

This work was carried out in collaboration among all authors. Author AA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author MA managed the analyses of the study, grammar correction, tabulation and revision work. Authors HB and VSC managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

A 75-year-old woman with a history of Type 2 Diabetes mellitus attended triage with complaints of nausea, occasional vomit, pain in epigastrium and some vague heaviness in breathing of 4-5 days duration. On her physical examination she had mild tachypnea, peripheral capillary oxygen saturation (SpO\textsubscript{2}) 92\% on room air, and high blood glucose and ketones respectively. She was evaluated and diagnosed to have bilateral submassive pulmonary Thromboemboli. She was managed with fibrinolytic treatment, Heparin, and supportive treatment along with management of Diabetic Ketoacidosis (DKA). Etiological examinations did not reveal any underlying cause. The contribution of diabetes and its acute complication, DKA, to the development of pulmonary thromboembolism is controversial and is discussed. This case with the presentation of sub-massive pulmonary embolism in a patient of DKA with no underlying cause identified is being reported owing to its rareness.
1. INTRODUCTION

The global diabetes mellitus prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 and the incidence of diabetic ketoacidosis (DKA) constitutes approximately 1% of diabetics [1]. Diabetes mellitus and hyperosmolarity is a known risk factor for arterial thrombosis. However, it is generally not recognized as an important risk factor for venous thromboembolism (VTE) [2,3]. Although there are several published case reports that describe this association, diabetes with hyperosmolarity is still not added to the list of acute medical illnesses associated with a high incidence of VTE.

The contribution of diabetes and its acute complication, DKA, to the development of pulmonary Thromboembolism is controversial, but it is thought to be associated with many factors. These include severe dehydration, high serum viscosity, thrombosis secondary to low cardiac output, diabetic coagulation and some defects in the fibrinolytic system which improves the activation and adhesion of thrombocytes, impaired fibrinolysis, increase level of plasminogen activator inhibitor-1, increase in level of coagulation factors associated with oxidative stress triggered by DKA, impaired endothelial integrity by hyperviscosity in endothelial cells and stasis occurring in the hypovolemia-induced vascular bed destroying vascular turbulence and increase thrombocyte activation and aggregation [4,5].

We herein report a case of a 75 year old female diabetic patient who was admitted with DKA and diagnosed to have submassive pulmonary thromboembolism (PTE). Her successful management and outcomes are discussed.

2. CASE REPORT

A 75-year-old lady with history of Type 2 Diabetes mellitus (T2DM) and on irregular treatment was brought to triage on 24/01/2020 with the complaints of nausea, occasional vomit, pain in epigastrum and some vague heaviness in breathing of 4-5 days duration. There was no history of chest pain, altered sensorium or seizures. She has no history of any other known co-morbidity or family history, recent surgery, recent trauma, long distance travel, or other strong known risk factors for Venous Thromboembolism (VTE). On examination, she weighed 60 kg (BMI 25.8 kg/m²); her pulse was regular 94 per minute, blood pressure 140/80 mm Hg, respiratory rate 24 per minute, peripheral capillary oxygen saturation (SpO2) 92% on room air and temperature 98.4°F. She was mildly dehydrated, looked unwell, and had mild pallor. There was no swelling in lower limbs and she was fully ambulatory. On systemic examination she had mild non tender hepatomegaly. Her rest of the systemic examination was essentially normal.

Initial labs in triage showed blood glucose concentration of 580 mg/dL, positive serum acetone (6 mmol/L) (normal <0.6 mmol/L), non specific 1 mm up sloping ST segment depression in anterior leads, normal troponin I and mildly raised B-type Natriuretic peptide (BNP), ABG show chronic respiratory alkalosis with A-a gradient 57 mm Hg on room air. Corrected serum sodium was 143 mEq/L and calculated serum osmolality was 364 mosm/Kg. She was diagnosed with diabetic ketoacidosis and shifted to high dependency unit (HDU) for further evaluation and management. She was treated with intravenous insulin infusion, intravenous fluids, antibiotics, and other supportive treatment. A routine 2D Echocardiogram showed D shaped LV cavity, mild tricuspid regurgitation with right ventricle systolic pressure (RVSP) of 58 mm Hg + right atrial pressure (RAP), Left ventricle ejection fraction (LVEF) 50% along with left ventricle diastolic dysfunction Grade 1. Her Glycosylated hemoglobin (HbA1C) was 12.1% suggesting poor glycemic control. She was advised computed tomography pulmonary angiography (CTPA) which was refused by the family. Few hours later she developed sudden respiratory arrest with bradycardia, transient momentary unconsciousness and a code blue was done. However, she recovered spontaneously within seconds and patient was shifted to medical intensive care unit (MICU). Her X-ray chest is shown in Fig. 1. There was no pulmonary infarct. Need of CTPA was further stressed and it was done which show evidence of bilateral, partially occlusive, pulmonary thromboemboli involving the main pulmonary artery branches and extending into the secondary and tertiary branches. (CTPA images in Fig. 2). Her lipid profile, kidney function tests,
liver function tests, thyroid stimulating hormone, vitamin B12, and bilateral venous Doppler study of lower limbs, iliac veins, renal veins and Inferior vena cava were unremarkable. Her other routine investigations show mild anemia (Hb 10 gm/dl), glycosuria (3+), and multiple cholelithiasis and a uterine fibroid on ultrasound abdomen. Her serology profile (Hepatitis B surface antigen, Hepatitis C antibody and Human immunodeficiency virus antibody 1 and 2) and thrombochek panel (Protein C activity, free protein S activity, Anti thrombin III activity, Factor V mutation detection, Homocysteine, and Lupus anticoagulant) were negative. She was administered a loading dose of unfractionated heparin (UFH) in dosage of 80 mg/Kg (5000 IU).

After shifting to MICU, and discussing about the role and need of thrombolytic therapy, she was administered tissue plasminogen activator (TPA alteplase) 100 mg in as per recommended systemic administration protocol. When infusion of the thrombolytic agent was complete, IV unfractionated heparin (UFH) infusion was started when activated partial thromboplastin time (aPTT) was less than twice its upper limit of normal. Post TPA, she had complaints of headache for which non contrast computed tomogram (NCCT) brain was done to rule out spontaneous intracerebral hemorrhage. It was unremarkable. Her headache responded to Paracetamol. Her activated partial thromboplastin time was monitored every six hourly and IV UFH heparin was continued in the dose of 18 IU/Kg. The dose was further modified as per heparin infusion nomogram to keep aPTT within therapeutic range. Once stable for 72 hours, she was transitioned to an oral agent Rivaroxaban in recommended dosage. She was discharged on 29/01/2020 on oral hypoglycemia drugs, Rivaroxaban, low dose aspirin, statins and supportive treatment. She has come in follow-up and is asymptomatic. She had been advised to get laparoscopic cholecystectomy electively.

3. DISCUSSION

Diabetes mellitus is a well-recognized risk factor for arterial thrombosis, however its relationship to venous thromboembolism (VTE) in adults is still debated. This case appears to be an incident of pulmonary embolism (PE) precipitated by diabetic ketoacidosis. The patient had no prior history of venous or arterial thromboses, no recent surgery or vascular intervention, no evidence of underlying deep venous thrombosis (DVT), hyperhomocysteinemia, abnormal thrombochek panel or any underlying medical or surgical condition known to be strongly associated with a higher incidence of VTE [6]. Despite the absence of obvious risk factors, she developed a PE, which was successfully treated with thrombolysis using tPA.

The case report supports hypothesis that patients with diabetes with hyperosmolarity have an increased risk of developing VTE. In one study the overall incidence of VTE among patients with hyperosmolarity was 1.7%, with 71% of the cases diagnosed during the index hospitalization, and 29% diagnosed during the 3 months after hospital discharge. In fact, the incidence of VTE in these patients with hyperosmolarity was very similar to the incidence among patients admitted for sepsis or acute connective tissue disease, medical conditions known to be strongly associated with a higher incidence of VTE [7].

The triad of endothelial injury, stasis or turbulence of blood flow and hypercoagulability, which plays an important role in venous Thromboembolism and was described by Virchow in 1856 and it, is still valid. Whatever the underlying causes, the formation of thromboembolism can be explained by Virchow's triad.
Diabetes is known as a hypercoagulability state and a risk factor for stroke and heart disease. It is associated with endothelial abnormalities, coagulation activation, hypofibrinolysis, and chronic platelet hyperactivity [8]. Acute hyperglycemia as is seen in DKA is believed to boost coagulation by its positive impact on factor VII and factor VIII activity as well as on tissue factor pathway inhibitor levels. Hyperinsulinemia also contributes as it increases plasminogen-activator inhibitor type 1 level, a substance isolated in disproportionate quantity in atheromatous material extracted from diabetic patients [8].

Hypercoagulable state in Diabetes mellitus is further enhanced in DKA. This could be explained by paradoxical platelet behavior, coagulation, endothelium activation, and diminution of the anticoagulation system [9]. Glycated hemoglobin (HbA1c), disrupts the oxygen-carrying function of hemoglobin and leads to the occurrence of capillary tissue hypoxia which in turn increases endothelial injury [4]. The presence of high levels of HbA1c in this case reminds us of the possibility of hypercoagulability on a chronic basis.

Although there are several published case reports of DKA with hyperosmolarity and DVT with VTE or major PTE but we could not find a case report of DKA with hyperosmolarity and without underlying DVT or other risk factors presenting as submassive PTE. This case illustrates the necessity of a high index of suspicion for thrombosis in patients with DKA and to consider the possibility of DKA as a risk factor, and in some cases, the underlying etiology for pulmonary thromboembolism. If future studies confirm our findings, DKA with hyperosmolarity will need to be added to the list of acute medical illnesses associated with a high incidence of VTE that deserve more intense thromboprophylaxis. Nevertheless, it is probable that coagulation abnormalities related to DKA translate into vascular events.

4. CONCLUSION
To conclude, clinicians must have high index of suspicion for thrombosis in patients of diabetic ketoacidosis as coagulation abnormalities seen in these patients may translate into vascular events and present clinically as acute crisis.

CONSENT
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her case study and other clinical information to be reported in the journal. The patients understand
that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


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