Fatal Pulmonary Thromboembolism in Patients with Diabetic Ketoacidosis: A Seven-Case Series and Review of the Literature

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ABSTRACT

Diabetes mellitus is a well-recognized risk factor for arterial thrombosis, however its relationship to venous thromboembolism (VTE) in adults is still debated. We report here seven cases of fatal pulmonary thromboembolism in adults with diabetic ketoacidosis as the underlying cause. In four of seven cases, there was no prior diagnosis of diabetes mellitus and patients were newly diagnosed either upon presenting to the hospital in diabetic ketoacidosis (DKA) or at the time of autopsy by the vitreous glucose concentration. None of the patients had family history, recent surgery, recent trauma, long distance travel, or other strong risk factors for VTE. Only two patients had a body mass index greater than 35 kg/m² and the same two cases had hospital stays that ranged from three to five days. We believe that DKA is a frequently unrecognized and sometimes overlooked risk factor for VTE, particularly in the forensic setting where routine toxicology and vitreous glucose analysis may not be standard practices. We encourage forensic pathologists, medical examiners, and coroners to consider the possibility of diabetic ketoacidosis as a risk factor, and in some cases, the underlying etiology for pulmonary thromboembolism. Additionally, we recommend vitreous glucose testing be performed if there are any signs of DKA or diabetes present, such as acetone in the blood. *Acad Forensic Pathol.* 2016 6(2): 198-205

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INFORMATION

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INTRODUCTION

Diabetes mellitus (DM) and related medical complications have become a major cause of death worldwide, with 382 million adults living with diabetes and that number projected to rise as a result of increasing obesity and aging (1, 2). It is a public health concern and an economic challenge to both industrialized and developing countries (3). A report by the Centers for Disease Control and Prevention (CDC) in 2011 estimated that nearly 26 million Americans have diabetes and estimated 79 million Americans have prediabetes (2).

Type 1 diabetes, which accounts for 5-10% of all cases, is characterized by cell mediated autoimmune destruction of pancreatic islet cells (β cells), resulting in insulin deficiency and hyperglycemia (2). Type 2 diabetes, has a strong association with metabolic syndrome and obesity, and is characterized by insulin resistance and inadequate insulin secretion, resulting in hyperglycemia. End-stage renal disease, diabetic neuropathy, retinopathy, vasculopathy, and coronary artery disease are long-term complications contributing to morbidity and mortality in diabetics, and most forensic pathologists are well acquainted with those conditions (4-6). Diabetic ketoacidosis (DKA) is a metabolic condition where the breakdown of fatty acids releases acidic ketone bodies thus lowering blood pH. Diabetic ketoacidosis and hyperosmolar hyperglycemia (also referred to as nonketotic hyperosmolar state) are characterized by dehydration and variable acidosis. While mortality related to DKA and hyperosmolar hyperglycemia has been decreasing over the last few years, both conditions can be fatal if not treated promptly (7, 8).

Venous thromboembolism (VTE) refers to a diagnosis of deep vein thrombosis (DVT) and/or pulmonary thromboembolism (PE) and is worldwide the third most frequently diagnosed cardiovascular disorder (9, 10). The incidence of VTE in the U.S. is one case per 1000 persons per year, with higher incidence in African-Americans and lower incidence in Asian-Americans (9, 11-13). While the age adjusted death rate for PE has significantly decreased, pulmonary thrombo-

emboli with or without deep venous thrombi are still a very common finding in the forensic setting (14). VTE is predominantly a disease of older adults and is rare in children and adolescents (10, 15, 16). Pulmonary thromboemboli usually arise from thrombi of the deep venous system of the lower extremities, but may also arise in the upper extremities, pelvic veins, renal veins, or the right heart (17). Some element of Virchow's triad (endothelial injury, stasis or turbulent flow, and hypercoagulability) is invariably present in most cases (18). The cause for pulmonary thromboembolism is often multifactorial, but recent surgery and trauma, immobility and venous stasis, obesity, pregnancy, malignancy, hereditary hypercoagulability, oral contraceptives, estrogen replacement, and smoking have been implicated as causative and/or contributing to the development of VTE (15, 19). Recurrence is also common and 30% of patients with VTE experience recurrence within ten years (9, 15, 20).

The relationship between diabetes mellitus and arterial disease is well documented and widely accepted, while the relationship between diabetes and venous thromboembolism is still debated. We present here two detailed case reports and a total of seven cases of fatal pulmonary thromboembolism diagnosed at the time of autopsy in patients with diabetic ketoacidosis.

CASE REPORTS

Case 1: A 47-year-old man with no known past medical history was found unresponsive by his landlord who had not seen him in two days. According to the landlord, the decedent had appeared ill and was holding his abdomen when last seen. He was pronounced dead by emergency medical personnel at the scene without resuscitation. On external exam, there was no evidence of trauma. No illicit drugs, prescription drugs, or alcohol were found at the scene. At autopsy, the decedent was an adult male with a body mass index (BMI) of 25 kg/m². The main finding and cause of death were bilateral, occlusive, loosely adherent pulmonary thromboemboli involving the main pulmonary artery branches and extending into the secondary and tertiary branches. There was no pulmonary infarct. The lower extremities were remarkable for deep

venous thrombi. Microscopically, both the pulmonary and lower extremity thrombi showed slight organization with peripheral fibrin and focal adherence to the vascular endothelium. There were no other significant gross findings. Toxicology results were positive for blood and vitreous acetone and isopropanol and a vitreous glucose concentration of 711 mg/dL, consistent with diabetic ketoacidosis. Molecular genetic studies were negative for sickle cell disease and negative for Factor V Leiden and prothrombin (Factor II) mutations (21).

Case 2: A 38-year-old man with a history of diabetes mellitus was brought to the emergency room by family members after complains of feeling dizzy and a witnessed collapse. Initial labs showed a blood glucose concentration of 521 mg/dL and positive serum acetone. He was diagnosed with diabetic ketoacidosis and was treated with subcutaneous insulin and intravenous fluids. Approximately five hours later, the patient complained of shortness of breath. He was found to be in pulseless electrical activity and despite advanced cardiac life support (ACLS), he expired. At autopsy, the decedent was a healthy appearing man with a BMI of 27.8 kg/m². There was no evidence of internal or external trauma. The main pulmonary arteries contained occlusive thromboemboli and dissection of the lower

extremities revealed intravascular thrombi in the deep veins of the left leg. Microscopically, both the pulmonary and deep venous thrombi were organizing with evidence of fibroblasts and adherence to the vascular wall. Vitreous toxicology revealed a glucose concentration of 191 mg/dL and molecular genetic studies were negative for Factor V Leiden G1691A mutation, Prothrombin (Factor II) G20210A and Methylene tetrahydrofolate reductase C677T (MTHFR) mutations.

Retrospective review of death certificates and autopsy reports in our office, from 2007 to 2014, revealed seven cases of fatal pulmonary thromboemboli in patients with diabetic ketoacidosis (**Table 1**). In all cases, the pulmonary thromboemboli were identified at the time of autopsy and were deemed to be the immediate cause of death. All cases (100%) had associated deep venous or calf vein thrombi. All individuals were male, ranging in age from 29 to 74 with six of seven cases being younger than 55 years old and only one patient above the age of 70 years (Case #5). Five decedents were black and two were Hispanic. Four out of seven individuals were not known to have diabetes and were diagnosed either upon presenting to the hospital in DKA (two cases; #1 and #2) or at the time of autopsy by vitreous glucose concentration (two cases, #6 and #7). Three individuals were known diabetics

Table 1: Summary of Seven Cases of Fatal Pulmonary Thromboembolism in Association with Diabetic Ketoacidosis

Case #	Age	Gender	Race	Body Mass Index (kg/m ²)	DVT	Known DM	Glucose Concentration (mg/dL)	HACVD	Genetics	Other Risk Factors
1	52	Male	Black	30	Yes	No	1000 (H)	HACVD	MTHFR	No
2	52	Male	Black	54	Yes	No	1384 (H)	-	-	3 days in hospital
3	34	Male	Black	40	Yes	Yes	800 (H)	ACVD	-	5 days in hospital
4	38	Male	Hispanic	27.8	Yes	Yes	521 (H)	ACVD	-	No
5	74	Male	Black	31.7	Yes	No	964 (H)	HACVD	-	No
6	29	Male	Hispanic	25	Yes	Yes	584 (PM)	HCVD	-	No
7	47	Male	Black	25	Yes	No	511 (PM)	-	-	No

DVT: Deep venous thrombosis

H: Hospital

HACVD: Hypertensive and atherosclerotic cardiovascular disease

ACVD: Atherosclerotic cardiovascular disease

DM: Diabetes mellitus

PM: Postmortem

MTHFR: Methylene tetrahydrofolate reductase mutation

HCVD: Hypertensive cardiovascular disease

who presented to the hospital with a chief complaint of weakness and were found to have elevated blood glucose and positive ketones. Body mass index (in kg/m²), as an indicator of obesity, was normal in three out of seven cases, 30-32 in two cases and >35 in only two cases (Cases #2 and #3). The same two individuals with BMI >35 had what could be considered as a prolonged hospital course (three and five days, respectively). Two cases (#1 and #5) had evidence of hypertensive and atherosclerotic disease manifested by cardiac and left ventricular hypertrophy and coronary artery atherosclerosis (CAD), respectively. Two cases (#3 and #4) had coronary artery disease and one case (#6) had hypertension but no evidence of CAD. Two cases (#2 and #7) had no evidence of either. Genetic analysis was negative in all but one case where a homozygous mutation for MTHFR was identified on postmortem testing (Case #1). Of note, our laboratory stopped testing and reporting the MTHFR C677T variant in 2013 because this variant was no longer recognized as a risk factor to thrombophilia based on the American College of Medical Genetics and Genomics (ACMG) recommendation (22). The two other gene mutations tested by our lab were G1691A mutation in the Factor V Leiden gene and the G20210A mutation in the Prothrombin (Factor II) gene. None of the decedents had any other major identifiable risk factors such as recent trauma, recent surgery, extended travel, or cancer. One patient (Case #6) had a history of remote blunt trauma to his leg, which upon further investigation was not thought to have been contributory. Substance abuse did not appear to contribute and routine toxicology for drugs of abuse was negative in all cases. Pulmonary thromboembolism was considered to be the mechanism of death in all cases presented, with diabetic ketoacidosis listed as the proximate (underlying) cause of death.

DISCUSSION

The relationship between diabetes and arterial vascular disease has been well established (5, 6). Diabetes mellitus increases the risk of developing coronary, cerebrovascular, and peripheral arterial disease via abnormalities in endothelial cells, vascular smooth muscle cells and platelets (23, 24). Metabolic abnor-

malities characteristic of DM, including hyperglycemia, increased free fatty acids, and insulin resistance contribute to decreased bioavailability of nitric oxide (NO), increased oxidative stress, and intracellular signal transduction abnormalities (25-28). Platelet function has been shown to be abnormal in DM (29). Several reports have suggested that diabetes mellitus, and diabetic ketoacidosis in particular, represent a prothrombotic state (25, 30-32). Carl et al. monitored the changes of protein C, protein S, von Willebrand factor (vWF), fibrinogen, homocysteine and folate in a group of young patients with DKA prior to, during, and following treatment (30). Their findings included a low concentration of protein C activity and free protein S prior to and during the first 24 hours of treatment. In addition, they found significantly increased concentrations of vWF antigen and vWF activity prior to treatment. Their hypothesis was that the metabolic insult of DKA initiates or further exacerbates the steady state of the vascular endothelial cells, with changes in the hemostatic profile resulting in a prothrombotic state, which then predisposes to the pathophysiology of cerebrovascular complications.

In a similar study, Bilici et al. investigated the hematological parameters (platelet count, white blood cell count, prothrombin time, partial thromboplastin time (PTT), bleeding time, coagulation time, protein C, protein S, antithrombin III, fibrinogen, D-dimer, factor VIII, factor IX, and factor X concentrations) at diagnosis and after treatment in 26 children with DKA (33). Increased platelet count, decreased PTT, low protein C, and high factor VIII concentrations were observed at diagnosis, indicating prothrombotic tendency. Following treatment, the platelet count was decreased, PTT was increased, and protein C and factor VIII concentrations returned to normal.

The relationship between diabetes mellitus and venous thromboembolism, however, is not as clear. Epidemiological studies have demonstrated a variable increased risk of VTE among diabetics (27, 34, 35). Stein et al. reported that in patients with DM who did not have obesity, stroke, heart failure or cancer, the relative risk of VTE was 1.52 in patients 20 to 29 years old and 1.19 in patients 30 to 39 years old,

suggesting that DM carries an increased risk for VTE which is apparent in younger patients in whom other comorbid conditions are less likely to be present (35).

In 2015, Gariani et al. conducted a systematic review and meta-analysis and concluded that the increased risk of VTE associated with DM results from co-founders rather than an intrinsic effect (36) and Bell et al. in a similar report concluded either no association or only a modestly positive one between DM and VTE in the general population (37). While arterial and venous thromboses have long been considered to be distinct entities with a different pathogenesis, some more recent reports have suggested that major risk factors for atherothrombotic disease, namely obesity, diabetes mellitus, hypertension, low HDL cholesterol and high triglycerides may also be associated with VTE (27, 38, 39). Whether arterial and venous thromboses do indeed represent completely separate entities or whether they are parts of a spectrum still remains to be determined (40).

In the meantime, single case reports and small case series of deep venous thrombi and pulmonary thromboemboli in children and adults with DKA have been published in the past few years. Quigley et al. reported the case of a 41-year-old man with new onset diabetes mellitus and ketoacidosis who underwent surgical embolectomy for treatment of right heart failure due to pulmonary thromboemboli (32). Worly et al. reported increased tendency for central venous catheter related thrombosis in children with type 1 diabetes mellitus and DKA (41). Sdogou et al. reported the case of a child with DKA and protein S deficiency who developed iliofemoral deep venous thrombi and pulmonary thromboemboli (42). Gill et al. reported the presence of axillary vein thrombosis in a 39-year-old male with trisomy 21 and DKA (43). Hegazi et al. reported a case of a 63-year-old diabetic who presented with DKA and was found to have a saddle pulmonary embolus which was successfully treated (44). Shujaat and Shapiro reported three cases of decompensated diabetic patients, one with hyperosmolar nonketotic hyperglycemia and two with diabetic ketoacidosis, who suffered pulmonary thromboembolism within 72 hours of admission (45). Both patients with DKA died

as a result of pulmonary thromboemboli on the second hospital day. More recently, Ozdemir et al. reported a case of a 57-year-old woman who was admitted with DKA and a pulmonary embolus, successfully treated with tissue plasminogen activator and found to have elevated homocysteine concentrations (46). Cherian et al. reported a case of a 21-year-old man with type 1 diabetes mellitus that developed multiple venous thromboses, including the renal vein, iliac veins and pulmonary vasculature, three days after admission for diabetic ketoacidosis due to non compliance with insulin therapy (31). A similar case of portal vein thrombosis in a patient with DKA was recently seen in our office.

The possible proposed mechanism(s) contributing to development of deep venous thromboses and pulmonary thromboembolism in diabetes and specifically in DKA have not been fully elucidated, but include some of the same mechanisms implicated in arterial thrombosis, namely abnormalities in coagulation factors, increased platelet aggregation, impaired fibrinolysis and endothelial injury due to hypertonicity (47-49). Also, severe dehydration associated with DKA may contribute by virtue of increased red blood cell rigidity and increased blood viscosity (50).

Establishing diabetic ketoacidosis as the underlying cause or a contributing factor of pulmonary thromboembolism should involve, in addition to the autopsy, a thorough investigation and exclusion of other causes or inciting events of a prothrombotic state. A detailed medical, family and social history should be obtained when possible, with a focus on recent trauma or surgery, recent long distance travel, substance abuse, and family history of VTE. Our belief is that there are likely more cases of pulmonary thromboembolism associated with the hyperglycemic state of diabetes mellitus (with or without ketoacidosis), which have been missed because vitreous toxicology was not routinely ordered in every case. It is conceivable that at least a fraction of the cases of pulmonary thromboemboli that are deemed idiopathic or of undetermined etiology are in fact associated with DM. A vitreous glucose toxicology test is relatively easy and inexpensive, and can be a valuable diagnostic tool in cases such

as these. Protocols could be established at toxicology labs to automatically test glucose concentration in vitreous humor if acetone or isopropyl alcohol is detected. Furthermore, in cases of VTE due to obesity alone, it is worth considering a vitreous glucose analysis, given the relationship between obesity and diabetes and the relative lack of routine medical care in many of our patients.

Cases of pulmonary thromboembolism in the presence of diabetic ketoacidosis and without any other identifiable risk factor should be certified as "Pulmonary thromboembolism (due to deep venous thrombi) due to diabetic ketoacidosis." If other risk factors are present, such as obesity, trauma, surgery, or prolonged travel with immobility, their contribution should be assessed on a case by case basis. For example, if the patient is obese but still relatively mobile, and presents with new onset diabetic ketoacidosis and pulmonary thromboemboli, obesity should be included as contributory but not necessarily as the underlying cause. In the absence of any traumatic or drug-related risk factors, the manner of these deaths would be natural. In the event of medication-induced DM/DKA complicated by PE, the death we would be deemed a therapeutic complication in New York City, and either as natural or accidental in jurisdictions where the manner of therapeutic complication is not an option.

CONCLUSION

We report here seven cases of fatal pulmonary thromboembolism in patients with diabetic ketoacidosis as the main predisposing factor and underlying cause. To our knowledge, this is the largest number of cases reported to date. The goal of this report is to highlight the relationship/association between DKA and VTE and to serve as a reminder to medical examiners and forensic pathologists to consider the possibility of DKA in the absence of other more typical risk factors for VTE.

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