

# A Case of Massive Pulmonary Embolism Due to Diabetic Ketoacidosis and Hyperhomocysteinemia

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## Abstract

A 57-year-old woman with no prior history was admitted to our emergency department with complaints of chest pain, dyspnea, xerostomia, syncope, and cyanosis on her lips and feet. On her physical examination, cyanosis, tachypnea, hypotension and sinus tachycardia were revealed. On the spiral computed tomography of the thorax of the patient with diabetic ketoacidosis, thrombus was detected in the left and right main pulmonary artery and segmental branches of the right pulmonary artery. The fibrinolytic treatment was initiated in the emergency department for the patient with hemodynamic shock due to the diagnosis of acute massive pulmonary embolism. Etiological examinations revealed B12 deficiency and hyperhomocysteinemia. This case, with the presentation of massive pulmonary embolism, resulted from the synergistic effect of hyperhomocysteinemia associated with B12 deficiency; hypovolemia caused by diabetic ketoacidosis was reported owing to its rareness.

**Keywords:** Diabetic ketoacidosis, hyperhomocysteinemia, pulmonary embolism

## INTRODUCTION

The prevalence of diabetes ranges from 2% to 6% in society and the incidence of diabetic ketoacidosis (DKA) constitutes approximately 1% of diabetics. Among the undiagnosed diabetics, the incidence of DKA is higher in the young and women (1). Diabetic ketoacidosis is placed top of the list of endocrinological emergencies, with its mortality rate varying between 1% and 10%.

According to the data of the United States of America (USA), the number of pulmonary thromboembolism (PTE) cases and associated mortality rate were estimated to be 600,000 and 60,000 per year, respectively. Pulmonary thromboembolism is an important cause of morbidity and mortality in the USA (2).

Many risk factors for PTE have been described (2). The contribution of diabetes and its acute complication, DKA, to the development of pulmonary thromboembolism is controversial, but it is thought to increase the tendency to severe dehydration, high serum viscosity and thrombosis secondary to low cardiac output (1).

Diabetic coagulation and some defects in the fibrinolytic system also increase the risk of thrombosis. Fibrinogen, which improves the activation and adhesion of thrombocytes, produces this effect by increasing the levels of factor VII, factor VIII, factor XI, factor XII, kallikrein and Von Willebrand Factor (vWF) and by impairing fibrinolysis, thereby increasing the level of plasminogen activator inhibitor-1 (3, 4). The level of coagulation factors associated with oxidative stress triggered by DKA increases and endothelial integrity is also impaired by hyperviscosity in endothelial cells (5). Stasis occurring in the hypovolemia-induced vascular bed destroys vascular turbulence and increases thrombocyte activation and aggregation.



Received Date: 19.11.2011

Accepted Date: 18.02.2012

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Eurasian J Pulmonol 2014  
DOI: 10.5152/ejp.2014.69345

• Available online at [www.eurasianj pulmonol.com](http://www.eurasianj pulmonol.com)

Hyperhomocysteinemia, which is another risk factor for pulmonary thromboembolism, results from B12 and folic acid deficiency and genetic enzyme defects in methionine metabolism. The level of homocysteine was found to be high in patients with DKA (5). Hyperhomocysteinemia is known to increase the risk of venous thromboembolism and it is thought that it produces this effect by leading to "down-regulation" of the endothelial thrombomodulin-protein C pathway (2). High homocysteine levels also have the effect of facilitating the formation of thrombi through many mechanisms including endothelial dysfunction, thrombocyte activation, the formation of cytotoxic reactive oxygen radicals, and lipid peroxidation (6).

Our patient is a massive pulmonary embolism case resulting from the synergistic effect of hyperhomocysteinemia associated with hypovolemia and B12 deficiency caused by DKA. To the best of our knowledge, this case of massive pulmonary embolism is the first in which DKA and hyperhomocysteinemia have been found to coexist and thrombolytic treatment has been performed.

#### CASE REPORT

A 57-year-old woman was admitted to our emergency department with the complaints of dyspnea, chest pain, syncope, cyanosis on her lips and feet, and xerostomia. The patient had a history of xerostomia for a long time and had suffered dyspnea while making any effort for the last a few days. Moreover, she had undergone cholecystectomy surgery 25 years ago. No other feature was found in addition to these medical histories. She had no recent trauma or operation, history of long-distance travel, obesity or smoking. The general medical condition of the patient was poor. Her arterial tension was 60/20 mmHg, her pulse was 120/min, and her respiration rate was 36/min. The smell of acetone on her breath was prominent, and she had peripheral cyanosis on her lips and feet.

The findings of laboratory examination were as follows: hemoglobin 11 gr/dL, hematocrit 35%, MCV: 111.9 f/L, MCH: 36.9 pg, RDW: 21.9%, blood glucose: 645 mg/dL, Na: 127 mmol/L, K: 3.9 mmol/L, Cl: 99 mmol/L, Hb A1c: 8.9% (3.6-5.8%), urinary ketone +3, and urinary glucose +4. At room temperature, the values of arterial blood gas were pH: 7.29, PO<sub>2</sub>: 63.3 mmHg, PCO<sub>2</sub>: 19.9 mmHg, HCO<sub>3</sub>: 9.5 mEq/L and SaO<sub>2</sub>: 88%. No finding was revealed on electrocardiogram except sinus tachycardia. Her chest radiography performed in a lying position was normal. Echocardiography revealed dilatation in right cardiac cavities, pulmonary hypertension and paradoxical movement of septum. On spiral computed tomography (CT) of the thorax, hypodensity consistent with thrombus was observed in the right and left main pulmonary artery and segmental branches of the right lower lobe pulmonary artery (Figure 1, 2). The patient was diagnosed with massive pulmonary embolism and DKA and thrombolytic therapy [100 mg t-PA(actilyse; Boehringer Ingelheim, Biberach, Germany); infusion every 2 hours], fluid replacement, insulin and dopamine treatment were initiated. A decreased concentration of potassium which occurred during DKA treatment was replaced and blood glucose regulation of the patient was provided through insulin therapy. The patient was heparinised after treatment and her therapy with oral warfarin continued until the international normalised ratio (INR) of 2-3 was reached. No complication was observed except minimal subcutaneous bleeding in the left femoral region.

As a consequence of laboratory examinations conducted for anemia etiology, hypersegmentation, hypochromia and anisocytosis were

observed on the peripheral blood smear of the patient. Her serum iron concentration and iron binding capacity were normal. After the level of vitamin B12 was found to be 121 pg/mL (140-950 pg/mL), a high dose of intramuscular B12 vitamin was added to the therapy. In the investigation for the etiology of PTE, p/c ANCA, ANA, anti DNA, APC resistance, antiphospholipid antibody level and protein C-S level evaluated after the end of anticoagulation treatment were normal. The concentration of homocysteine was found to be 26.74 micromol/L (N: 5-15 micromol/l). Tumour markers and abdominal CT results were normal for the patient whose father had the history of colon carcinoma.

A rapid progress was observed in the clinical and laboratory findings of the patient and she was discharged from hospital with oral warfarin, insulin and vitamin B12 treatment.

#### DISCUSSION

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 is still valid.

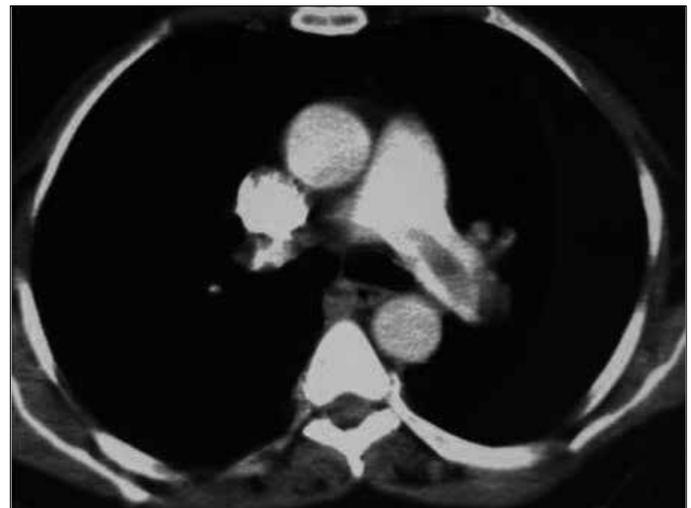


Figure 1. Thrombus in the left main pulmonary artery

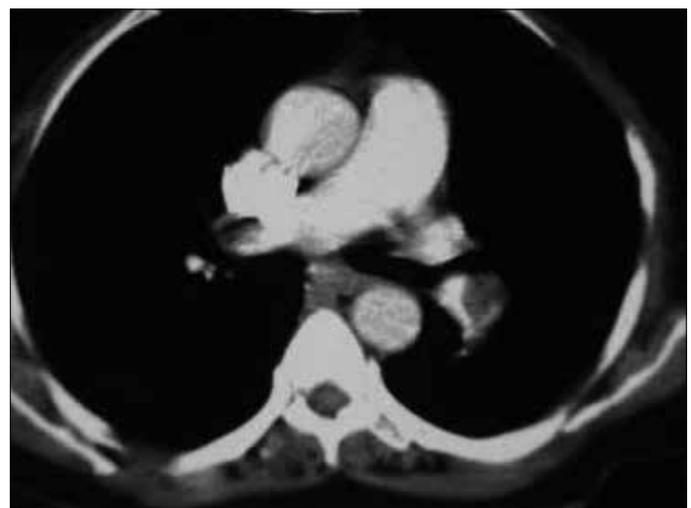


Figure 2. Thrombus in the right main pulmonary artery and the right lower lobe segmental branches

Whatever the underlying cause, the formation of thromboembolism can be explained by these mechanisms (2).

In diabetic patients, vascular endothelial integrity, which provides the primary defence against thrombus, is impaired. Fibrinogen is high in diabetics at the level of factor VII, factor VIII, factor XI, factor XII, kallikrein and vWF, and these coagulation factors increase the activation and adhesion of the thrombocytes, as well as blood viscosity. Low levels of Protein C in diabetic patients increase the tendency to coagulation. An increased level of plasminogen activator inhibitor factor-1 leads to impairment in fibrinolysis in these patients. In addition, the levels of some factors increasing thrombocyte aggregation were found to be higher in diabetic patients (3, 4).

According to a study by Carl et al. (5), in DKA, the activity of protein C decreased considerably and the levels of fibrinogen, homocysteine and vWF increased; however, these factors recovered with DKA therapy. In our patient, the levels of fibrinogen and homocysteine were high, but post-treatment protein C level was normal. Carl et al. (5) emphasised the contribution of vascular endothelial injury associated with oxidative stress caused by acidosis to the formation of thrombus. Changes in the turbulence of blood flow induced by hypovolemia caused by the effect of hyperglycemia and DKA can increase the thrombocyte aggregation and adhesion and lead to impaired endothelial integrity (1, 7). In our patient, DKA may have triggered thrombosis by hypercoagulability and its effect of increasing stasis, thus causing massive PTE.

To the best of our knowledge, only one other case of major PTE triggered by DKA has been published to date and surgical treatment was performed rather than the thrombolytic treatment used in this case (8).

Although some studies suggest that diabetes does not increase the risk of thromboembolism, the risk of venous thromboembolism was found to be higher in diabetic patients than in non-diabetic patients in one study (4). Glycated hemoglobin (HbA1c), which is formed by glycated proteins due to hyperglycemia, disrupts the oxygen-carrying function of hemoglobin and leads to the occurrence of capillary tissue hypoxia. This is an effect that increases endothelial injury (7). The presence of high levels of HbA1c in our study reminds us of the possibility of hypercoagulability on a chronic basis.

Vitamin B12, with folic acid in the methylation of homocysteine to methionine, is an essential cofactor in the conversion of methylmalonyl coenzyme A into succinyl coenzyme A. In 95% of patients with vitamin B12 deficiency, an increase is observed in the levels of serum homocysteine and methylmalonic acid (9). Although it is not definitely known, high levels of homocysteine in diabetic patients increase the risk of thrombus by leading to the disruption of endothelial integrity (6).

Homocysteine decreases the level of protein C. It is already known that hyperhomocysteinemia is an important risk factor for thrombosis and atherosclerotic vascular disease (2).

In the study conducted by Oger et al. (10), vitamin B12 deficiency was stated to be a risk factor for venous thromboembolism. In our patient, the increased level of homocysteine appeared to be associated with B12 deficiency. However, a high level of homocysteine may be a factor in other diabetic patients (5, 6).

## CONCLUSION

Our case supports the fact that diabetes and hyperhomocysteinemia increase the risk of venous thromboembolism and prompted us to think that massive pulmonary embolism associated with dehydration caused by DKA may develop. Early diagnosis and thrombolytic treatment in indicated cases can decrease the rate of mortality.

**Ethics Committee Approval:** N/A.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-review.

**Author Contributions:** Concept - B.Ü., L.Ö., O.N.H., B.Ö., E.Ç.E.; Design - B.Ü., L.Ö., O.N.H., B.Ö., E.Ç.E.; Supervision - B.Ü., L.Ö., O.N.H., B.Ö., E.Ç.E.; Resource - B.Ü., L.Ö.; Materials - B.Ü., L.Ö.; Data Collection&/or Processing - B.Ü., L.Ö.; Analysis&/or Interpretation - B.Ü., L.Ö., O.N.H.; Literature Search - B.Ü., L.Ö.; Writing - B.Ü.; Critical Reviews - B.Ü., L.Ö., O.N.H.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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