CASE REPORTS

Acute Limb Ischaemia in a Septic Patient with Diabetic Ketoacidosis

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ABSTRACT

This is a patient with septicaemia and diabetic ketoacidosis who developed an acute ischaemic lower limb from an arterial thrombus. The patient had decreased protein S function.

Keywords: Limb ischaemia in DKA

Isquemia Aguda de Miembros en un Paciente Séptico con Cetoacidosis Diabética

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RESUMEN

Se trata de un paciente con septicemia y cetoacidosis diabética que desarrolló una isquemia aguda en un miembro inferior a partir de un trombo arterial. El paciente presentaba función disminuida de la proteína S.

Palabras claves: Isquemia de miembros por CAD

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INTRODUCTION

Decreased immune reactivity is present in diabetes mellitus [DM] (1). One abnormality of the immune system in diabetes is defective polymorphonuclear leucocyte chemotaxis (2). Thus patients with diabetes mellitus are at increased risk of infection. We have previously reported that 74% of patients who present with hyperglycaemic states have bacteraemia (3). Bacteraemia activates coagulation pathways and thus predisposes a septic individual to thrombosis. Diabetes, by itself is a hypercoaguable state, and the hyperglycaemic states of diabetic ketoacidosis can result in thrombosis and disseminated intravascular coagulopathy [DIC] (4–6). Acute limb ischaemia from thrombosis is more frequently seen in hyperosmolar hyperglycaemic states (7), and although rarely seen in diabetic ketoacidosis [DKA], is one of the potentially devastating complications. In 2005, Zisper reported a case of acute aorto-iliac and femoral artery thrombosis complicating diabetic ketoacidosis (8). We report the case of a patient presenting in DKA and septicaemia, who developed an acute ischaemic lower limb and had a prothrombotic disorder.

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CASE REPORT

A 43-year-old female police officer, was previously well until 2 weeks prior to presentation, when she presented to her physician with a history of vomiting of recently eaten food and generalized dull abdominal pain. A diagnosis of a urinary tract infection was made by a primary care physician and metamizole sodium, trimethoprin-sulphamethoxazole and paracetamol were prescribed. Polyuria, polydipsia, a low grade fever and anorexia subsequently developed. There were no complaints of sore throat and no cardiorespiratory or neurological symptoms. The random glucose was said to be high. This prompted referral to the University Hospital of the West Indies (UHWI). Of note, there was a one-year history of anaemia supposedly secondary to menorrhagia from leiyomyoma, but she was non-compliant with haematinics. Both her mother and brother had diabetes mellitus. There was no family history of venous thromboses. There was no history of cigarette smoking or use of illicit drugs or alcohol. A monogamous relationship with condom use was documented.

On presentation to UHWI, there was no evidence of cardiopulmonary distress. The BMI was 27.9 kg/m^2, the blood pressure 113/71 mmHg, the pulse rate 126 beats per minute (bpm) and the respiratory rate 28 breaths per minute with a temperature of 38.44° celsius and the pulse oximeter read 96% on room air. There was the smell of ketones on her breath, temperature was 39°C and the pulse oximeter read 96% on room air. The urinary ketones were increased. The mucus membranes were pale and very dry, and there were white exudates on the oropharynx. The cardiovascular examination was normal. Respiratory examination was significant for markedly decreased air entry at the left lower zones. Abdominal examination revealed a pelvic mass which was consistent with her leiyomyoma. Her neck was supple and cranial nerves including fundoscopy and motor system examination were normal, except for absent ankle reflexes. There was decreased sensation to light touch and pinprick as well as vibration at the L_5/S_1 distribution.

The assessment of diabetic ketoacidosis (DKA), sepsis secondary to urinary tract infection and left lobar pneumonia, oral candidiasis with an immunocompromised state, symptomatic anaemia and overweight were made.

Investigations are reported in Table 1. Initial urinalysis revealed 4^+ ketones with trace protein only. Serial blood glucose monitoring was done at this point. Intravenous insulin was given and then basal/bolus insulin with, amoxicillin/clavulanic acid 1.2 grams intravenously every eight hours, and nystatin 100 000 units orally every six hours and prophylactic heparin subcutaneously, 5000 units twice daily. Two units of packed red blood cells were transfused.

Table 1: Investigations

Hb 7.3 g/Dl, MCV-65 FL, WBC – 19,100/uL	Neutrophil count – 83%
Platelet – 726 000/uL	ESR – 15 mm/hour
Blood film– target cells, hypochromia	
Sodium 130 mmol/L, potassium 5.7 mmol/L, chloride 104 mmol/L	bicarbonate 10 mmol/L, urea 5.5 mmol/L, creatinine 78 umol/L,
Glucose 40.3 mmol/L (725.4 mg/dL).	The calculated anion gap was 16.
Arterial blood gas unavailable	Liver function tests normal
HbA1c – 15%	HIV negative; stool cultures negative

The first blood culture grew microaerophilic streptococci. Subsequent serial blood cultures were negative. The urine culture grew group B streptococci. The sputum culture grew acinetobacter species. The chest X-ray revealed a homogenous opacification with a meniscus and blunted cardiophrenic and costophrenic angles, most likely due to a left pleural effusion. Electrocardiogram revealed sinus tachycardia.

On day 3 of admission, the patient complained of coldness in her right foot. On examination the dorsalis pedis pulse was decreased. An arterial Doppler ultrasound revealed absent blood flow in the saphenofemoral, popliteal, posterior tibialis and dorsalis pedis arteries. Embolectomy was unsuccessful on the first and second attempts. Despite intravenous and intra-arterial heparin, the clot persisted. A third embolectomy was attempted, and the subsequent arterial Doppler ultrasound then revealed minimal blood flow in the saphenofemoral and popliteal vessels, but not the distal vessels. Cytology of the evacuated clot revealed a thrombus with embedded polymorphs. No organisms were obtained on culture. Transthoracic echocardiogram was normal. The limb became gangrenous on day 14 of admission and a below knee amputation was performed 21 days after her admission. A thrombophilia screen revealed that her protein S function was 31% (normal 60−120%) and the protein S antigen was 115% (normal 58–150%). The protein C level was normal at 72% (64−120%). These were done prior to the initiation of warfarin therapy but during thrombosis and heparin therapy. Her mammogram and Pap smear were normal. Repeat chest X-Ray showed worsening of the left pleural effusion by the 6^{th} day of admission and on thoracocentesis, pus was obtained. An empyema was diagnosed, with resultant perisplenic collection. Both collections were drained and streptokinase was used for the empyema, with future plans for Video Assisted Thoracoscopy.

DISCUSSION

Infections are a source of morbidity and mortality in diabetes mellitus. They account for 22% of deaths in this population (9). The innate immunity is the body's first line defence against microbial infection, but this is impaired in diabetes mellitus (10). Many studies have demonstrated decreased functions (chemotaxis, phagocytosis and respiratory burst) of the polymorphonuclear cells of subjects with diabetes when compared to non-diabetic subjects. There is decreased complement levels and cytokine response after stimulation and microbes thrive in the hyperglycaemic milieu (11). Diabetes mellitus suppresses neutrophils and may cause oral candidiasis, as in the index case (12). Of the series of patients with hyperglycaemic states and bacteraemia, 13% had the aerotoleant organism, Microaerophilic Streptococci, which have been implicated in pyogenic abscess formation and empyema (13). In bacteraemia, seeding is not uncommon. In 15% of

patients with diabetes, seeding in bacteraemia has been documented (14). Although Marantic arterial emboli have been previously reported in diabetic subjects (15), it was not felt that the arterial thrombosis in this patient was due to marantic arterial embolization.

Sepsis is a malignant, intravascular and hypercoagulable state. The initial source of infection was the urinary tract which precipitated the DKA. The latter disorder further predisposed her to a state of overwhelming sepsis, resultant bacteraemia, then empyema with subsequent perisplenic abscess. Diabetic hyperglycaemic emergencies are also procoagulable states. Elevated levels of pro-inflammatory cytokines and lipid peroxidation markers, as well as procoagulant factors such as tissue factor, plasminogen activator inhibitor (PAI-1) and C-reactive protein (CRP) have been demonstrated in DKA. The levels of these factors return to normal with insulin therapy and correction of hyperglycaemia (16).

Although, it is the hyperglycaemic hyperosmolar state that has been reported to be more frequently associated with arterial thrombosis, there have been reported cases in patients with DKA, where thrombocytosis has been also documented and activation of inflammatory mediators has been quite increased (8). DKA and sepsis may have precipitated the thrombocytosis and arterial thrombosis, limb ischaemia and ultimately limb loss in the index case.

Protein S is a vitamin-K dependent anticoagulant protein, which functions as a cofactor to facilitate the action of activated protein C on its substrates, activated factor Va and factor VIIIa. Protein S deficiency which was first discovered in 1979, can be congenital (autosomal dominant) or acquired, for example, in liver disease or during warfarin therapy. Protein S deficiency is usually associated with venous thromboembolism, in persons below the age of 45 years [2% in the unselected population and up to 6% in patients with recurrent thrombosis and family history of thrombosis] (17). The case discussed did not have a family history of venous thromboses, but one still wonders if she may coincidentally always have had the deficiency. Protein S deficiency was noted in our patient before warfarin therapy was instituted. This patient had arterial thrombosis, not quite fitting the picture, and Protein S levels can fall in the setting of acute thrombosis and surgery (18). The association of her protein S deficiency with arterial thrombosis is at best weak. Another seldom recognized cause for acquired protein S deficiency is sickle cell anaemia; however, this condition alone does not produce a thrombophilic state (19). This patient did not have a sickle cell screen.

In summary, the authors believed that the hyperglycaemic and immunocompromised states along with sepsis and DKA predisposed this patient to arterial thrombosis and limb loss. This finding of protein S deficiency in this case might have been coincidental and pre-existent.

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