OC Okafor (*)
SO Ike (**)

(*) Department of Morbid Anatomy
(**) Department of Medicine
University of Nigeria
Teaching Hospital
Enugu, Nigeria

Correspondencia:
Dr. Okafor OC
Department of Morbid Anatomy
University of Nigeria
Teaching Hospital
PMB 01129, Enugu, Nigeria
Postal Code: 400001

Telf: +234 80 33 309 085
Fax: +234 42 256 962
E-mail: *okechukwu.okafor@gmail.com*

Stress-related massive gastrointestinal bleeding in a diabetic and obese woman following double leg amputation.

Foot ulceration is a leading cause of hospital admission for patients with diabetes mellitus and the main reason for major amputation. This study presents the rare association of double amputation of both legs within 16 months of each other, a rarer outcome of diabetic foot ulcer disease, and the fatal complication of massive stress-related gastrointestinal bleeding the occurred thereafter leading to haemorrhagic shock and sudden death. On an index patient the clinical management was reviewed, a detailed autopsy performed after demise, and an extensive literature review including MEDLINE searches were carried out. Autopsy study revealed 3 ulcers in the gastric body and 1 in the gastric antrum measuring between 0.5 and 1cm and associated with about 2.5 litres of clotted blood in the gastrointestinal lumen extending from the stomach to the sigmoid colon. The patient combined physical stress factors for gastric ulceration which include uncontrolled diabetes mellitus prior to amputation, massive trauma from lower limb amputation with delayed wound healing, intake of non-steroidal anti-inflammatory drugs in the setting of past medical history of successfully treated peptic ulcer disease and the emotional stress factor of depressive illness related to the loss of her second lower limb. This association has not been reported in literature and with this we wish to warn clinicians to look out for this fatal complication in managing patients with advanced diabetic foot ulcer disease especially those going for a second limb amputation.

Palabras clave: Stomach, stress ulcer, haemorrhagic shock, diabetic foot ulcer disease

INTRODUCTION

There is an ever-present demand to optimize diabetic care because of the growing number of people with non-insulin dependent (type 2) diabetes mellitus and the attendant heavy burden of vascular disease, chronic morbidity and premature death associated with this condition (Harris, 1993; King and Rewers, 1993; Zimmet, 1993). Significant in this regard is the need for much greater involvement at every level of people with diabetes themselves and the setting out of some precise, evidence-based, achievable targets, to reduce by one-half the diabetes-related amputation rates, among others (World Health Organization and International Diabetes Federation, 1990; Home and Hallet, 1996).

Foot ulceration is a leading cause of hospital admissions for patients with diabetes and an extremely expensive complication of diabetes mellitus. The prevalence of foot ulceration in community-based surveys of diabetic individuals ranges from 5 to 10.2 % (Neil et al., 1989; Moss et al., 1992; Young et al., 1994). The feet are a major site of peripheral neuropathy leading to sensory deficit and autonomic dysfunction. Ischaemia often results from atherosclerosis of the leg vessels, which in the diabetic is often bilateral, multisegmental and distal, involving arteries below the knee. Infection often complicates ulceration in both the neuropathic and ischaemic foot, with eventual overwhelming tissue destruction. This is the main reason for major amputation in diabetic patients (Edmonds et al., 1986; Thomas et al., 1991).

This study presents an adult Nigerian woman with eventual double amputation of both legs within 16 months of each other, a rarer outcome of diabetic foot ulcer disea-

se, and the fatal complication of massive stress-related gastrointestinal bleeding that occurred thereafter.

MATERIALS AND METHODS

Our study was done using an index patient presenting with a rare clinical association. We reviewed the clinical management, performed a detailed autopsy study after her demise, and also carried out an extensive literature review including MEDLINE searches on this association of clinical features.

The patient is a 71-year-old woman, a known hypertensive and diabetic of more than 10 years. She had been on metformin, glibenclamide and lisinopril, but was not compliant. She first presented to our medical unit in 2004 and was managed for diabetic foot ulcer disease which eventually resulted in a below-knee amputation of the left leg on 27th July, 2004.

She presented again 13 months later on 29th August 2005 with right leg ulcer of 5 days duration. The lesion started as blisters which coalesced, ruptured and later ulcerated, discharging pus. She had no antecedent history of trauma, burns, insect bites or fever. She had stopped alcohol intake two years previously and did not use tobacco in any form. There was no known family history of hypertension, diabetes mellitus or sudden death.

Clinical examination revealed an ill-looking, elderly, obese woman, with waist-hip ratio of 1.1:1 (the Body Mass Index [BMI] could not be assessed because of her state of health, with an already amputated lower limb). She had a below-knee amputated left leg and pitting leg oedema up to the knee on the right leg. There was an extensive ulcer covering the lower 2/3 of the antero-lateral surface and lower 1/3 of the posterior surface of the right leg. The pulse rate was 102 beats/minute, normal volume and regular (of the brachial pulse). The brachial, carotid, femoral and popliteal pulses were present but the radial pulses on both upper limbs, the right dorsalis pedis and right posterior tibial pulses were not palpable. The blood pressure was 120/60mmHg right arm supine and 110/60mmHg left arm supine. The jugular venous pulsation was not raised and the apex beat could not be localized (due to patient?s obesity). The heart sounds, 1st and 2nd only, were heard and were of normal intensity, with no cardiac murmurs.

She had neurological deficits of absent right plantar response, pin prick, light touch and cold temperature sensations on S1, L4, L5 dermatomes. Her fasting blood glucose was 229mg/dl. An impression of poorly controlled diabetes mellitus in a known hypertensive, with diabetic right leg ulcer and below-knee amputation of the left leg, was made. Investigations were ordered both initially and at varying stages of her clinical management. These are shown in Table 1.

She was placed on intravenous ceftriaxone, ciprofloxacin and oral ciprofloxacin; intravenous, and later oral metronidazole, intramuscular tetanus toxoid, oral low dose aspirin; oral lisinopril ranging from 2.5 to 7.5mg and withdrawn (at a later stage); oral frusemide and spironolactone; oral non-steroidal anti-inflammatory drugs (NSAIDs) particularly piroxicam and ibuprofen, diazepam and amitriptyline, at different stages of her 12 weeks stay in the hospital, based on her clinical status and laboratory investigation. She was on intravenous infusion initially (normal saline), and after surgery and had courses of Fansidar® (sulphomethoxazole-pyrimethamine) and dihydroartemisin treatment for malaria during the course of her admission.

She was on subcutaneous three times daily insulin for good glycaemic control and was transfused with 4 units of fresh whole blood after initial packed cell volume (PCV) reading of 20 % with clinical anaemia, 3 unit of blood peri-operatively, and 3 more units of whole blood by the 3rd day post- surgery.

She received intravenous hydrocortisone as part of her resuscitative armamentarium during post-operative hypotension and terminally.

Multidisciplinary team care, involving the managing medical team, the orthopaedic surgeons, the dieticians and the physiotherapists, was in place throughout the patient?s hospitalization. Wound care of the ulcerated right leg was maintained with initial wound incision and drainage, daily wound dressing with eusol and hydrogen peroxide solutions, as well as surgical debridement. The latter revealed extensive gangrene of the entire right leg, with Wagners Grade 5 classification. Above-knee amputation of the right lower limb was proposed to the patient after due explanation of the implication and the prognosis if not carried out.

It took up to the 9th week of admission to convince and psyche up the patient on the need to have the surgery be-

cause of her depressive state. Findings during surgery included extensive gangrene involving the muscles, blood vessels and other soft tissues up to the thigh of the right lower limb, and atherosclerotic changes of the right femoral artery. Wound healing with good granulation tissue formation progressed satisfactorily, for the next three weeks post-operatively, except for a small portion of the anterior skin flap over the stump, which was necrosed. With catheterisation, patient's daily urine output was above 2 litres, and consistently above 1 litre post-operatively.

However, on the morning of 21st November, 2005, in the 12th week of admission, after sleeping well the previous night, and taking her breakfast with her medications, the patient was noticed to be depressed and singing melancholic songs. Her fasting blood glucose was 99mg/dl. The attention of the unit was later drawn to her suddenly sweating profusely, with cold extremities, temperature recording 35oC and thready pulse. Her blood pressure had sunk to 80/50mmHg and her respiratory rate was 34 cycles/min. Her fluid input/output chart the preceding 24 hours had recorded input of 3,000mls and output of 2,450mls, respectively. Resuscitative measures were commenced, but the patient eventually gave up and was confirmed clinically dead at 9.25am.

RESULTS

At autopsy, general examination confirmed obesity and a sub-umbilical surgical scar extending to the pubic symphysis. There was a raw amputation wound at the lower end of the right thigh which is foul-smelling and dirty in some areas (see Figure 1). A well-healed surgical scar on the left leg was seen which corresponds to the earlier amputation a year before.

The most severe pathological changes were observed in the gastrointestinal tract. The gastrointestinal lumen from the stomach to the sigmoid colon was completely filled with clotted blood and corresponds to approximately 2.5 litres of blood (see Figure 2). Close examination of the entire mucosa revealed 3 ulcers in the body (see Figure 3) and 1 in the antrum of the stomach. These are sharply demarcated and measure between 0.5cm and 1cm. The floor of the ulcers are dark (haemorrhagic) and the edges of the largest 2 are slightly elevated; the gastric wall was not perforated and the peritoneum was clean. There was thinning out of the mucosa and loss of ruggae in the fundus and body of the stomach (see Figure 3).

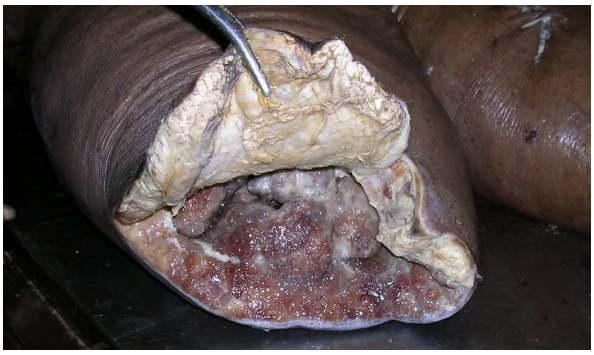

Figura 1.— Second amputation wound (right leg) showing granulation tissue on the lower surface and necrotic tissue with poor healing on the upper surface.

Histology confirmed peptic ulcers in the stomach; the latter associated with reactive fibrosis in the floor and wall and extending to the submucosa. Some medium-sized blood vessels with ruptured walls were seen beneath the ulcer base. The intact gastric mucosa in the body showed mild chronic gastritis with severe glandular atrophy. Helicobacter pylori organisms were not found. The rest of the gastrointestinal mucosa did not show any morphological alteration.

A plethora of morphological finding were also seen in other organs, most of which are related to the underlying poorly controlled diabetes mellitus condition prior to the admission and are listed in Table 2.

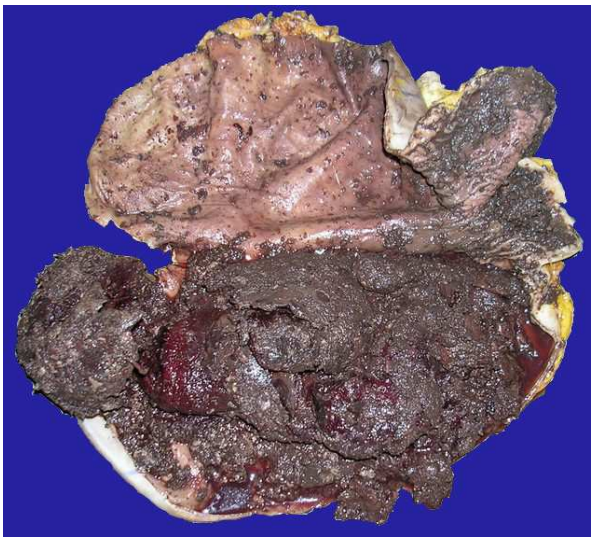

Figura 2.— Stomach with the lumen filled with clotted blood.

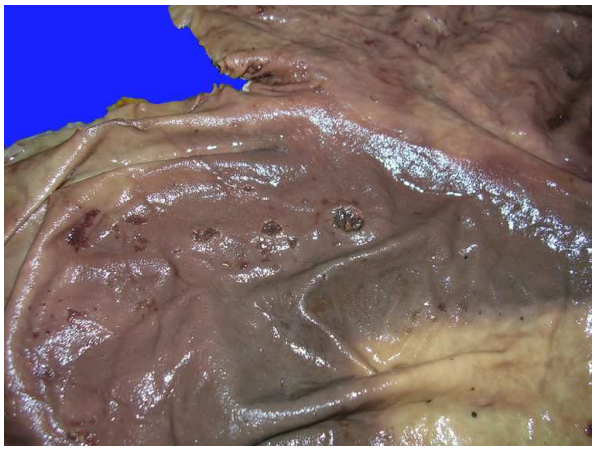

Figura 3.— Gastric body mucosa showing 3 ulcers with slightly raised edges; also note the loss of the normal gastric ruggae.

DISCUSSION

Early recognition of the "at risk" foot, the prompt institution of preventive measures, and the provision of rapid and intensive treatment of foot complications in multidisciplinary foot clinics have reduced the number of amputations in diabetic patients (Edmonds et al., 1986; Edmonds et al., 1997). The burden of diabetic foot disorders transcends not only the bed-days spent in the hospital, but also the trauma of amputation, psychological aftermath, financial drain, and death. In 1986-87 diabetic foot disease accounted for 20.8 % of the total bed-days attributed to diabetes in the North-Western Region of the United Kingdom, while the average healthcare cost for a diabetic patient undergoing lower limb amputation in the United States of America in 1985 was $24,700 (Reiber, 1992; Williams, 1994).

One of the most important advances in diabetic foot care is the increasing success with bypass grafts to the dorsalis pedis artery which has led to the decline in amputations (Logerfo et al., 1992). This is a corrective surgical option that should be aggressively pursued to mitigate the physical, psychological, financial and mortality burden imposed by limb amputations, much so double-limb amputation.

Perhaps more than all else is the contribution of the informed and motivated diabetic patient to health outcomes, that patient education can never be overemphasised (Assal and Visser, 1995). This will, among other things, include the need for drug and clinic compliance as well as proper foot care, as borne out from our index patient. This is what has led to the concept of diabetes teams in Europe (Diabetes Integrated Care Evaluation Team, 1994), to help drive the point of adequate patient education home to the ?grassroots? where the people live and work.

The term stress-related gastrointestinal tract bleeding (SRMD) represents a continuum of conditions ranging from stress-related injury (superficial mucosal damage) to stress ulcers (focal deep mucosal damage). Both extremes of the continuum are caused by mucosal ischaemia, and both show a propensity for the acid-producing corpus and fundus (Spirt, 2003). Caused by mucosal ischaemia, SRMD is most commonly seen in critically ill patients in the intensive Care Unit (ICU) (Spirt, 2004). Stress-related gastric ulceration has been studied in a wide variety of clinical conditions including acute pancreatitis (Cosen-Binker et al., 2004), recurrent peptic ulcer (Yamamoto et al., 2000), ingestion of NSAIDs and other medications (Hochain et al., 1995; Pulanic et al., 1998; Wu et al., 2000), alcohol abuse (Suzuki et al., 1998), portal hypertension (Khodadoost and Glass, 1972), and physiologic stress associated with hospitalization in an ICU for severe life-threatening disease or trauma (Chamberlain, 1993; Peterson, 1995). Bleeding, even if it is only occult, defines acute stress-related gastrointestinal tract bleeding (SGIB). The rates of SGIB vary according to the inclusion criteria: 13 to 100 % microscopic SGIB, 2.3 to 9.5 % haemorrhage with blood transfusion and/or shock (Malledant et al., 1989). Although physical stresses are known to induce gastric ulcers with bleeding, little is known about the influence of emotional stress on upper gastrointestinal bleeding. Aoyama et al. reported that with the Hanshin-Awaji earthquake that occurred in Japan in January 1995 the induced life event stress not only triggered but also exacerbated gastric ulcer, particularly in the elderly (Aoyama et al., 1998).

We here present an uncommon clinical case of massive gastrointestinal haemorrhage leading to haemorrhagic shock and death in a patient with physical stress factors for gastric ulceration which include uncontrolled diabetes mellitus prior to amputation, massive trauma from lower limb amputation with delayed wound healing, intake of NSAIDs in the setting of past medical history of successfully treated peptic ulcer disease as well as the emotional stress factor of depressive illness of the loss

of her second lower limb. It took several weeks of her hospital admission and the co-operation of family members and the medical team to palliate this depressive state and convince her of the dire necessity of this second leg amputation. The autopsy findings of 4 deep ulcers with raised edges measuring between 0.5cm and 1cm in the stomach as well as the loss of the gastric ruggae support the interpretation of stress-related reactivation of a pre-existent peptic ulcer diathesis. The bleeding was acute and progressed rapidly because there was no history of melaena stool or haematemesis while she was on hospital admission prior to death.

Stress-related gastrointestinal bleeding could be fatal, especially when it is undiagnosed (Steinberg, 2002; Metz, 2005). This case exemplifies such a scenario. We wish to raise the awareness that massive stress-related gastrointestinal bleeding is one of the serious complications of diabetic foot ulcer disease and clinicians should look out for it even when overt clinical features of gastrointestinal bleeding are not yet observable. Prevention is the best treatment for the stress-related ulcer, and this prevention may occur at both a primary level (reduction of gastric acid and/or bleeding) and a secondary level (placation of emotive or physical precipitators) (Friedman and Martin, 1993; Tryba and Cook, 1997). Depression and negative perception of life events have been shown to be important risk facts in development of and reactivation of peptic ulcer disease (Walker et al., 1988). The psychological trauma of a gangrenous foot, the thought of possible loss of one or both lower limbs, and the amputation itself are important stress factors for gastrointestinal bleeding and should be borne in mind while managing these patients. The patient in our case could have benefited from more family support and from more psychotherapy. We recommend judicious use of NSAIDs and thorough evaluation for current or past peptic ulcer disease for these patients. Depending on the degree of suspicion faecal occult blood analysis and/or endoscopy should be carried out with a view to early diagnosis.

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ICONOGRAFÍA

TABLE 1: Laboratory investigations

FBC, ESR			Serum E/U/Cr/Ca/PO4				Urinalysis		
	6/9/05	28/9/05		5/9/05	29/9/05	13/10/05		2/9/05	13/10/05
PCV	28%	29%	Na^+	134mmol/L	138	135	Appearance	Cloudy	Pale yellow, clear
WBC	14,000/mm³	8,500/mm³	K^+	3.9mmol/L	3.9	3.6	pH	Alkaline	Alkaline
N	92%	78%	HCO_3^-	26mmol/L	29	27	Protein	+	Trace
L	8%	20%	Cl^-	100mmol/L	103	99	Sugar	++++	Nil
E	-	2%	Urea	3.2mmol/L	4.0	4.2	Acetone	Nil	Nil
			Cr	74 mol/L	79	62	Bile	Nil	Nil
			Ca^{2+}	2.0mmol/L	-	2.4	WBC	20/hpf	15/hpf
			PO_4^+	1.1mmol/L	-	1.0	RBC	8-10/hpf	5/hpf
							Cellular casts	+++	Nil

Repeat PCV	
26/9/05	20%
06/10/05	40% (PT)*
27/10/05	32% (PT)*
11/11/05	35% (PT)*

Lipid Profile (29/9/05)	
Cholesterol	3.6mmol/L
HDL	0.5mmol/L
LDL	2.5mmol/L
VLDL	0.6mmol/L
TGL	0.6mmol/L

Urine m/c/s (6/9/05)

Coliform bacilli >10^5cful/ml. Sensitve to Augmentin Nitrofurantoin. Resistant to Gentamicin, Nalidixic acid, Cotrimoxazole, Amoxycillin.

Coagulation profile	
PTT	33 sec
Control	30 sec
Range	25 – 35 sec
PT	14 sec
Control	13 sec
Ratio	1:1

ECG (14/10/05)

Sinus rhythm rate 100/min; Normal P wave in II but biphasic in V_1. Normal PR interval. Indeterminate axis. Normal QRS duration, ST&T segment and QT interval

Fasting Blood Glucose (FBG)
Initial – 229mg/dl
Subsequent daily checks with glucometer, with euglycaemic levels maintained from the 6th week.

Wound Swab m/c/s

6/9/05	10/10/05	11/11/05
Mixed growth of *Staph. aureus* and non-lactose fermenting bacilli both sensitive to Augmentin, Drovid, Siprosan, Ofloxacin. Resistant to Amoxycillin, Gentamycin. Cotrimoxazole,	Coliform bacilli sensitive to Ciprofloxacin, Ceftriaxone, Gentamicin. Resistant to Augmentin, Ofloxacin	Non-lactose fermenting bacilli sensitive to Gentamicin Ciprofloxacin. Resistant to Amoxycillin, Augmentin, Ofloxacin

* (PT): Post transfusion

Tabla 1

Table 2: Summary of autopsy findings	
Gross finding	**Histology/comments**
Lungs: Heavy (right 750g; left 650g)	Alveolar capillary congestion (shock lung).
Heart: Enlarged (700g); left (1.8cm thick) and right (0.6cm) ventricular hypertrophy	The patient had been a known hypertensive for more than 10years and not compliant with anti-hypertensives. The hypertension may be related to the bilateral adrenal cortical adenomas.
Aorta and elastic arteries: Calcified plaques	Severe atherosclerosis. Contributory factors here include hypertension, diabetes mellitus, obesity, and advanced age of the patient.
Coronary arteries: Plaques; without significant reduction of luminal size	Moderate atherosclerosis.
Spleen: Enlarged (500g) with homogenous meaty-red cut surface	Chronic passive congestion probably related to right heart failure.
Liver: Enlarged (2,800g)	Chronic passive congestion (panlobular) probably related to right heart failure; atrophy of hepatic plates in zone 3; moderate portal lymphocytic infiltrate.
Gall bladder: Numerous (21) multifaceted yellowish stones filling the lumen	Calculous cholecystitis (cholesterol stones). The risk factors in this patient are obesity and diabetes mellitus.
Kidneys: Enlarged (300g each); pale cortex; several staghorn-shaped calculi in the pelvis and calices measuring between 2cm and 4cm	Diffuse cortical necrosis due to acute ischemic tubular necrosis; interstitial oedema and features of benign nephrosclerosis: fibroelastic hyperplasia in the large arteries and onion-skin hyperplasia in the intermediate-sized ones
Adrenal glands: Each has a 2cm, rounded, yellow mass in the cortex.	Cortical adenomas
Vertebral column: Osteophytes in 1st to 5th thoracic vertebrae	Osteoarthritis

Tabla 2

ABBREVIATIONS: *NSAIDs*: Non-steroidal anti-inflammatory drugs. *PCV*: Packed cell volume. *BMI*: Body Mass Index. *SRMD*: Stress-related mucosal disease. ICU: Intensive Care Unit. *SGIB*: Stress-related gastrointestinal tract bleeding.