

Insulin-induced Oedema in a Patient with Diabetes Mellitus Complicated by Ketoacidosis

Alphonsus N. Onyiriuka, Frances A. Ehirim

Department of Child Health, University of Benin Teaching Hospital, Benin City, Nigeria.

Correspondence mail:

Endocrine and Metabolic Unit, Department of Child Health, University of Benin Teaching Hospital. PMB 1111, Benin City, Nigeria. email: alpndiony@yahoo.com.

ABSTRAK

Dalam artikel ini, kami melaporkan sebuah kasus baru yakni seorang anak perempuan Nigeria berusia 15 tahun dengan berat badan yang sangat kurang (29 kg) dan didiagnosis dengan diabetes melitus tipe 1 sejak empat tahun yang lalu, yang gagal kontrol dan datang dengan ketoasidosis diabetikum. Pengendalian kadar gula darahnya buruk karena kepatuhan pasien yang buruk. Pada hari kelima sejak masuk rumah sakit, terjadi pitting edema yang tidak terasa nyeri tanpa disertai perubahan warna kulit di pergelangan kaki. Perjalanan alami edema yang diinduksi oleh insulin ditemukan pada pasien ini yakni edema membaik dalam waktu tujuh hari kemudian tanpa diberikan terapi spesifik, misalnya dengan pemberian diuretik. Penyebab utama edema generalisata pada anak-anak dan dewasa muda, misalnya kwashiorkor, sindroma nefrotik, sirosis hati, gagal jantung kongestif dan glomerulonefritis akut dapat disingkirkan berdasarkan hasil anamnesis, pemeriksaan fisik dan pemeriksaan laboratorium yang relevan. Setelah semua penyebab utama edema disingkirkan, maka disimpulkan bahwa terapi insulin merupakan penyebab edema yang ditemukan pada pasien kami. Tujuan penulisan artikel ini adalah untuk mengkaji ulang kepustakaan medis tentang edema yang diinduksi oleh insulin dan meningkatkan kesadaran para klinisi mengenai hal ini. Kesimpulan, edema yang diinduksi oleh insulin perlu dipertimbangkan sebagai diagnosis banding edema pada anak dan dewasa muda dengan diabetes melitus tipe 1 yang disertai oleh komplikasi ketoasidosis, terutama bila pasien tersebut mempunyai berat badan kurang.

Kata kunci: terapi insulin, efek samping obat, edema, diabetes melitus tipe 1, dewasa muda.

ABSTRACT

In this article we reported a recent case of a 15-year-old grossly underweight (29kg) Nigerian girl diagnosed of type 1 diabetes mellitus four years ago and who defaulted from follow up but presented with diabetic ketoacidosis. Glycaemic control was poor because of poor compliance. On the 5th day on admission, a non tender pitting oedema without skin discolouration developed over the ankles. The natural history of insulin-induced oedema was observed in this patient since the oedema resolved seven days later without any specific therapy, such as administration of diuretics. The major causes of generalized oedema in childhood and adolescence, such as kwashiorkor, nephrotic syndrome, liver cirrhosis, congestive heart failure and acute glomerulonephritis were excluded by findings from the history, physical examination and relevant laboratory investigations. Having excluded these major causes of oedema, the obvious conclusion was that the insulin therapy was the cause of the oedema observed in our patient. The aim of this article is to review existing medical literature on the subject of insulin-induced oedema and raise the awareness of clinicians on the subject. In conclusion, insulin-induced oedema should be considered in the differential diagnosis of oedema in children and adolescents with type 1 diabetes mellitus complicated by ketoacidosis, particularly if they are underweight.

Key words: insulin therapy, adverse drug reaction, oedema, type 1 diabetes mellitus, adolescence.

INTRODUCTION

Insulin is indispensable in the treatment of type 1 diabetes mellitus (T1DM). Insulin-induced oedema is not adequately recognized. More importantly, most cases have a mild course and improve spontaneously, resulting in underreporting.^{1,2} At present, the pathogenesis is poorly understood and its epidemiology is largely unknown. It affects mainly patients with newly diagnosed T1DM or patients with poorly controlled diabetes mellitus after starting intensive insulin therapy or grossly underweight patients on large doses of insulin.^{3,4} Reports of occurrence of insulin-related oedema in patients with diabetic ketoacidosis (DKA) is very few.^{5,6} Its clinical presentation is quite variable ranging from mild peripheral oedema (majority of cases) to cardiac failure and massive serosal effusions.⁷ DeFronzo et al.^{8,9} in two separate reports, have attempted to clarify its underlying pathophysiologic mechanism by demonstrating insulin-induced antinatriuresis in man. Although insulin-induced oedema is usually self-limiting, persistence or recurrence or progression to overt cardiac failure or development of pleural effusion can occur occasionally.^{4,5} Reported weight gain in insulin-related oedema has ranged from 1.8 to 20kg.^{10,11} Sometimes, too, the oedema may be gradually replaced by fat tissue with persistent weight gain.¹²

A survey of available standard textbooks of Paediatrics¹³ as well as Paediatric Endocrinology¹⁴ revealed that there is no reference to insulin in a discussion of differential diagnosis of oedema. In addition, oedema is not mentioned in the list of complications of insulin therapy. The poor awareness among clinicians concerning insulin therapy in the differential diagnosis of oedema was further confirmed during an Update Course in Paediatrics for Resident Doctors from various training centres in Nigeria who were shown a case of insulin-induced oedema in an adolescent girl being treated for diabetic ketoacidotic coma for discussion. None of the 20 candidates mentioned insulin-induced oedema in their discussion of the differential diagnosis of the oedema in this patient.

The purpose of this report is to review the scanty existing medical literature on the subject

of insulin-induced oedema and to raise awareness of clinicians that oedema may be observed during insulin therapy.

CASE ILLUSTRATION

The patient is a 15-year-old adolescent Nigerian girl who was diagnosed of type 1 diabetes mellitus four years ago. Compliance with therapy has been poor because of lack of support from the father and some misconception on the part of the patient and her mother, resulting in a poor glycaemic control. Before she defaulted from follow up, she was on premixed combination of human insulin 70% intermediate-acting insulin plus 30% short-acting (regular) insulin given twice daily (20 units in the morning and 10 units in the evening).

The patient presented with abdominal pain and fever of one day duration, difficulty in breathing of 8 hours duration and loss of consciousness of 5 hours duration. No history of jaundice, chest pain, palpitation, cyanosis, or smoky or frankly bloody urine. She has not achieved menarche.

Physical examination revealed an acutely ill-looking adolescent girl who was pyrexial (temperature 39.6°C) and dehydrated. No facial puffiness or oedema of the limb. She was underweight (weighed 29kg) with a sexual maturity rating of Tanner stage 1. She was unconscious with global hypotonia and hyporeflexia. Abdominal reflexes were absent. No evidence of diabetic retinopathy. Her pulse rate was 148/minute, regular and good volume. Blood pressure was 100/60 mmHg (50th percentile for age and height). Heart sounds were normal. No cardiac murmur. She was tachypnoeic (rate 34 cycles/minute) and dyspnoeic with acidotic breathing. Lung fields were clear on auscultation. Laboratory investigations showed blood glucose 18.2mmol/L (327mg/dl), ketonuria 3+, and acidosis (bicarbonate 10 mmol/L), confirming diabetic ketoacidosis. Serum electrolytes values were normal except for the bicarbonate. Serum levels of creatinine and albumin were 0.7 mg/dl and 3.6 g/dl respectively. Urinalysis did not reveal any significant proteinuria or bilirubinuria or haematuria. Glycosuria was present (2+) and urine pH was 5.0. Full blood count, peripheral

blood film and chest radiograph were normal. The liver function test was essentially normal. Blood culture yielded no growth. Dehydration was corrected with normal saline (0.9% sodium chloride). She was treated with insulin infusion at a rate of 0.1 unit/kg/hr and standard protocol for management of diabetic ketoacidosis was followed.^{11,12} Insulin infusion was discontinued on the 2nd day of admission and replaced with subcutaneous insulin (soluble) at 1 unit/kg/day 6 hourly. Antibiotics I.V. Ceftriaxone and I.V. Gentamycin were administered. She regained consciousness between the 5th and 6th hour of treatment and the fever subsided on the 4th day of admission. On the 5th day on admission, a non-tender pitting oedema without skin discolouration developed over the ankles (**Figure 1**). The weight has increased by 5kg (from 29 kg on admission to 34 kg). A repeat serum creatinine level was normal and a repeat urinalysis did not reveal proteinuria or bilirubinuria. Repeat urea and electrolytes revealed normal values including bicarbonate level. Urine output remained adequate. The patient and her mother were counselled on the importance of compliance with therapy. The oedema resolved over the next seven days without any specific medical intervention, such as administration of diuretics.



Figure 1. Shows bilateral pitting insulin oedema of the legs in an adolescent girl with T1DM complicated by ketoacidosis.

She discharged from the ward after spending 14 days on admission and is currently being followed up in paediatric endocrine-metabolic clinic of the hospital. As at the last clinic visit one month ago, there is no history of recurrence of insulin oedema in our patient.

DISCUSSION

The diagnosis of insulin-induced oedema in this patient was based on: (i) the exclusion of all other major causes of generalized oedema in childhood and adolescence, such as kwashiorkor, nephrotic syndrome, liver cirrhosis, congestive heart failure, and acute glomerulonephritis; (ii) its temporal relationship to improved glycaemic control and resolution of diabetes ketoacidosis and; (iii) its benign nature as evidenced by its spontaneous resolution. Kwashiorkor was unlikely because of the age of the patient (15 years) and absence of dermatitis, hair changes or mental apathy. Serum albumin level was normal. The clinical features against nephrotic syndrome include absence of ascites, no oedema before commencement of insulin therapy, no proteinuria and normal serum albumin level. Against the diagnosis of liver cirrhosis as the cause of the oedema was the negative history of jaundice now and in the past and no history of bleeding. Physical examination revealed no jaundice, ascites, or distended superficial abdominal veins. No bilirubinuria. Congestive heart failure was unlikely because of absence of cardinal signs of heart failure, such as tachypnoea, tachycardia, dyspnoea, tender hepatomegaly. There was no raised jugular venous pressure or basal crepitation in the lungs. Chest radiograph did not show any evidence of cardiomegaly or pulmonary oedema. Acute glomerulonephritis was excluded because the negative history of smoky or frankly bloody urine. Oliguria and hypertension were also absent. Urine microscopy did not reveal red blood cells. Other causes of generalized oedema include over hydration, hyponatraemia and aspirin sensitivity. The patient was not receiving intravenous fluid or aspirin and the serum sodium concentration was within normal limits, thus making them unlikely in the differential diagnosis of oedema in our patient. Oedema appeared following improved

glycaemic control with insulin infusion and the oedema resolved spontaneously without any specific medical intervention, indicating its transient/benign nature. Diuretic therapy may be indicated in severe decompensated cases.¹⁵ In cases refractory to diuretic therapy, ephedrine may be indicated.⁴ From the foregoing, insulin therapy was the most probable cause of the oedema in our patient. Our diagnostic approach in this case was therefore in keeping with the view of Kalambokis et al.¹¹ which stated that insulin-induced oedema is a diagnosis of exclusion.

Some of the epidemiological observations in our patient were in tandem with those of previous reports and need consideration. Consistent with the observation in previous reports^{1,3-5}, our patient is a female adolescent with marked underweight, suggesting that female gender and underweight are risk factors for the development of insulin-related oedema in adolescence. The natural outcome of insulin-induced oedema was observed in our patient since no specific medical intervention was instituted before the resolution of the oedema. These observations are in keeping with the reports of previous studies.^{2,6,10,15} In contrast, there are also reports of resolution of oedema following specific therapies, such as administration of loop diuretics¹⁵ or ephedrine.⁵ However, in that report, the clinicians did not observe their patient for spontaneous resolution. The clinical implication is that in cases where the oedema fails to resolve spontaneously, loop diuretics and/or ephedrine may be administered. Similarly, Suzuki et al,¹⁶ reported four cases with diabetes mellitus due to the 3243 mitochondrial tRNA-mutation who developed oedema of the lower extremities following glycaemic control and their oedema responded to administration of Co-enzyme Q 10. On the 5th day on admission, a non-tender pitting oedema without skin discolouration developed over the ankles. The oedema resolved spontaneously seven days later. A review of the literature revealed that duration of the insulin therapy before onset of oedema as well as duration of oedema before spontaneous resolution varied widely. Reports indicate that the duration of insulin therapy before onset of oedema ranged from 1-14 days^{1,6,12,15} while the

duration of oedema before resolution ranged from 4-10 days.^{1,12,15} In the index case, both the duration (5 days) of insulin therapy before onset of oedema and duration (7 days) of oedema before resolution were in keeping with previous reports.^{1,6,12,15}

Although insulin-induced oedema has been recognized for a long time as an uncommon complication of insulin therapy, its pathogenesis remains poorly understood. Several mechanisms have been proposed by different authors. Intensive fluid resuscitation in an individual with insulin-deficient catabolic state may lead to extravasation of fluid into the subcutaneous tissue, resulting in peripheral oedema.¹⁵ Some authors have suggested that it may involve vasomotor changes induced by the rapid glycaemic control or that a rapid improvement of glycaemic control might have induced hepatic re-oxygenation, resulting in the production of reactive oxygen species in the liver that ultimately contribute to cell damage and increased capillary permeability.¹⁷ Other authors think that renal tubular sodium reabsorption is enhanced by insulin therapy via two mechanisms; stimulating the sodium/potassium-ATPase and the expression of Na⁺/H⁺ exchanger 3 in the proximal tubules.^{11,18} In addition, transient inappropriate hyperaldosteronism has also been suggested as a contributing factor to the fluid retention following insulin therapy.¹¹ Spark et al.¹⁹ in their study demonstrated that inhibition of glucagon with insulin treatment decreased renal excretion of sodium and fluid. It is interesting to note that many patients with insulin-induced oedema described in literature were significantly underweight.^{2,12,20,21} Our patient was markedly underweight. Thus, further confirming this clinical observation. One lesson from the index case is that underweight patients with T1DM with poor glycaemic control are particularly at risk of insulin-induced oedema and caution should be taken when insulin therapy is intensified in these circumstances. Better recognition of insulin-induced oedema and its spontaneous improvement without any specific treatment would decrease concern about this clinical condition and thus, prevent unnecessary interventions.

CONCLUSION

Insulin-induced oedema should be considered in the differential diagnosis of oedema in children and adolescents with type 1 diabetes mellitus complicated by ketoacidosis, particularly if they are underweight.

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