JKAU: Med. Sci., **Vol. 19** No. 3, pp: 97-102 (2012 A.D. / 1433 A.H.)
DOI: 10.4197/Med. 19-3.8

A Case Report: Insulin-Induced Edema in a 13-Year-Old Girl

Abdulmoein E. Al-Agha, FRCPCH and **Ali H. Ocheltree,** MBBS
Department of Pediatrics, Faculty of Medicine
King Abdulaziz University
Jeddah, Saudi Arabia
aagha@kau.edu.sa

Abstract. A 13-year-old girl with type one *diabetes mellitus* poorly controlled for seven years, presented with total body edema and rapid weight gain (7 kg in 10 days). The edema developed one week after the initiation of an intensive insulin treatment. Initially, it started as lower limb edema; other causes of edema were excluded. With current trends toward intensive insulin therapy, clinicians need to be aware of the existence of Insulin Edema Syndrome. Its occurrence needs be documented and differentiated from other causes of edema.

Keywords: Adolescents, Insulin-induced edema, Type 1 diabetes.

Introduction

Peripheral or generalized edema is an uncommon complication of insulin therapy, which is rarely reported and has been termed as insulin edema[1]. The first pediatric record of such a case was in 1979 [2], since then, few cases were described[3,4]. Although rare as it may be, it must be differentiated from other causes of edema, such as cardiac or renal disease, which may themselves arise independently or as a complication of *diabetes mellitus* (DM). It is mainly initiated in patients with newly diagnosed or poorly controlled (DM) after starting intensive insulin therapy and in underweight patients on large doses of insulin. The

Correspondence & reprint request to: Dr. Abdulmoein E. Al-Agha
P.O. Box 80215, Jeddah 21589, Saudi Arabia
Accepted for publication: 29 October 2011. Received: 14 September 2011.

pathophysiology remains obscure, although the condition is self-limiting, progression to overt cardiac failure and development of pleural effusion has been reported[5]. With current trends toward intensive insulin therapy, clinicians need to be aware of the existence of Insulin Edema Syndrome. This report describes a case of insulin edema in a poorly controlled adolescent girl.

Case Report

A 13-year-old Saudi girl admitted with a history of generalized edema for ten days. The edema started in her lower extremities, then advanced into a total body edema including neck and face with no peri-orbital edema; there was also a rapid weight gain (7 kg in 10 days). On admission, her height was 145 cm (25th centile) and weight was 46 kg (50th centile). She was on pubertal Tanner stage IV, and had regular menses. She was not febrile, had a sinus tachycardia of 100/min, blood pressure of 110/80 mmHg and respiratory rate of 23/min. Physical examination revealed mild generalized non-pitting edema involving the upper thighs, buttocks, back, neck and face, and no pallor. There was a strong family history of DM in her maternal uncles and her father. She had a severe episode of diabetic ketoacidosis, which required admission to the intensive care unit. After recovery, she was started on intensive basal / bolus insulin therapy shifting her from her usual conventional therapy of two injections per day. Two weeks later, a non-tender, non-itchy, non-pitting edema without skin discoloration developed in her lower limbs. The edema deteriorated on the second day and was progressive till the time of her presentation. Laboratory investigation revealed high blood glucose of 360 mg/dl, glucosuria, but no ketonuria and no proteinuria, and an elevated glycosylated hemoglobin A1C concentration of 12.9% (normal range 4.5-6%). Serum albumin was 37 g/L (34-50 g/L) and total protein was 80 g/L (64 0 82 g/L). An echocardiogram revealed an ejection fraction of 60% and no evidence of heart failure. Chest X-ray revealed no pleural effusion. Liver enzymes were elevated, AST was 52 U/L (15 - 37 U/L), ALT was 108 U/L (30 - 85 U/L) and ALP was 254 U/L (50 - 136 U/L). Patient serum cholesterol was high 7.82 mmol/L (0 - 5.2 mmol/L) and triglycerides were normal 1.34 mmol/L (0.3 - 2.3 mmol/L). Hepatic serology, for hepatitis B and C viruses, was negative. An abdominal ultrasound revealed hepatomegaly and no ascites. Patient thyroid function test was normal with a TSH of

0.906 uIU/L (0.27 - 4.2 uIU/L) and a free T4 of 13.78 pmol/L (12 - 22 pmol/L). Serum microalbuminuria was elevated 852 mg/L (0 - 20 mg/L). Upper thighs and buttocks ultrasound revealed streaky areas of fluid accumulation at the deep subcutaneous tissues, bilaterally and symmetrically (Fig. 1). During her hospital admission, a satisfactory glycemic control was achieved on a daily insulin dosage of 1.5 U/kg. Insulin was given in her upper arms to avoid the edematous lower limbs. Gross non-pitting edema persisted all over the body. Frusemide was started at a daily dose of 40 mg/day. Upon completion of Frusemide administration, a one month follow-up period was uneventful, as the edema disappeared.

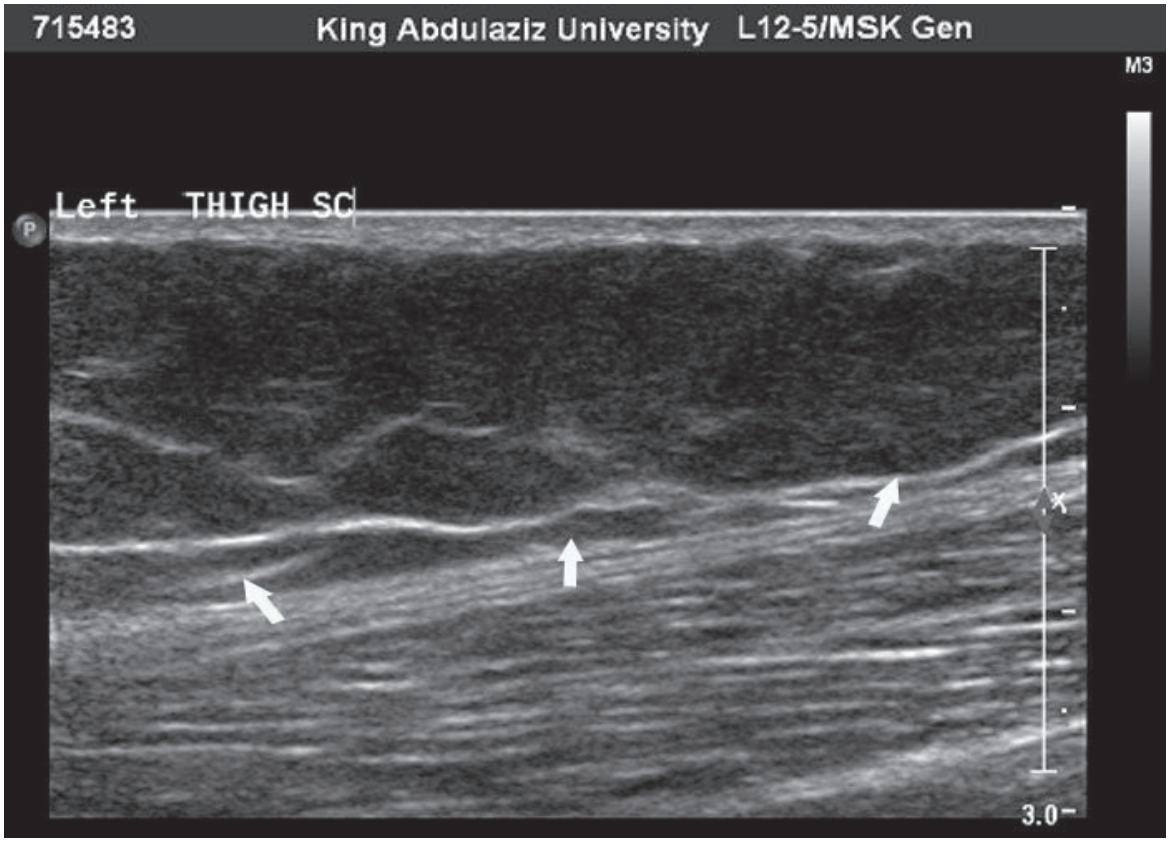

Fig. 1. An ultrasound of the left thigh; at the level of the femur, both medially and longitudinally was seen. There are linear anechoic areas in the deep subcutaneous tissues (arrows) representing fluid accumulation, just anteromedial to the femur bone.

Discussion

A female adolescent, with a body mass index of (18.5 kg/m^2) and substantial weight gain of 7 kg over 10 days prior to her presentation,

developed insulin edema that evolved gradually as her insulin doses were increased rapidly to control her long lasting poor glycemic state. The incidence of insulin-induced edema in children with type 1 DM is unknown. Because of its benign nature, it is probably underreported. Considering the differential diagnosis for the new occurrence of edema in the current case, there was a wide array of etiologic possibilities, which were all excluded. Including, ischemic cardiomyopathy in the setting of diabetic dyslipidemia, hypothyroidism, nephrotic syndrome, hepatic dysfunction, or the overzealous replacement of free water during the fluid resuscitation phase of her diabetic ketoacidosis.

Several theories regarding the pathophysiology of insulin-induced edema formation were proposed, the most popular explanation is, overzealous fluid resuscitation in the setting of an extreme catabolic state[6]. Both renal glomeruli and proximal renal tubules play an important role in insulin clearance[7]. Under normal circumstances, the renal tubular capacity to excrete filtered insulin is enormous, and saturation does not occur. When the proximal tubules are damaged by acute or chronic renal failure, urinary insulin clearance is increased and results in an increased insulin requirement[7].

Shaper[2,3] speculated that the sudden retention of water by the glycogen-laden tissue may also be a possible mechanism of acute insulin-induced edema[8]. Other mechanisms include the interplay of various hormones such as antidiuretic hormone (ADH), glucagon, and aldosterone. Persistently, elevated (ADH) concentrations during chronic hyperglycemia can cause fluid retention and an inability to excrete a water load during volume repletion[9]. Poor glycemic control is also associated with elevated glucagon, which inhibits the effect of circulating aldosterone[9]. Rapidly achieving glycemic control may result in the fall of circulating glucagon concentrations, therefore, removing the inhibitory effect on aldosterone and causing fluid retention. Chronic hyperglycemia has been associated with increased capillary permeability, which may also contribute to edema formation[9]. Generally, when spontaneous resolution does not occur within a few days, treatment with diuretics and ephedrine has been shown to be beneficial[10].

Insulin-induced edema should be considered in patients newly diagnosed with or have poorly controlled DM after starting intensive insulin therapy. The exact mechanism is not clear. The natural history of

insulin edema is self-limiting and usually resolves over the course of several days to few weeks. Though, progression to overt cardiac failure and the developments of pleural effusion were reported[5]. With current trends toward intensive insulin therapy, clinicians need to be aware of the existence of Insulin Edema Syndrome. Its occurrence should be documented and differentiated from other causes of edema as it can be confirmed by ultrasound. Insulin-induced edema could be prevented by a gradual increase in the insulin dosage and avoidance of hypoglycemia.

References

[1] **Leifer A.** A case of insulin edema. *JAMA* 1928; **90**(8): 610-611.

[2] **Shaper AG.** Parotid gland enlargement and the insulin-oedema syndrome. *Br Med J* 1966; **1**(5490): 803-804.

[3] **Shaper AG.** The insulin-oedema syndrome in African diabetic subjects. *Trans R Soc Trop Med Hyg* 1966; **60**(4): 519-525.

[4] **Hirschberg B, Muszkat M, Marom T, Shalit M.** Natural course of insulin edema. *J Endocrinol Invest* 2000; **23**(3): 187-188.

[5] **Sheehan JP, Sisam DA, Schumacher OP.** Insulin-induced cardiac failure. *Am J Med* 1985; **79**(1): 147-148.

[6] **Sharon M, Cassoria FG, Rose SR, Loriaux DL.** Edema associated with improved glycemic control in an adolescent with type 1 diabetes. *J Pediatr* 1987; **111**(3): 403-404.

[7] **Rabkin R, Ryan MO, Duckworth WC.** The renal metabolism of insulin. *Diabetologia* 1984; **27**(3): 351-357.

[8] **Júlíusson PB, Bjerknes R, Søvik O, Kvistad PH.** Generalized edema following insulin treatment of newly diagnosed *diabetes mellitus*. *Tidsskr Nor Laegeforen* 2001; **121**(8): 919-920.

[9] **Cotellessa M, Mazzella M, Mulas R, Caratozzolo A, Romano C.** Insulin edema in three adolescents with insulin-dependent *diabetes mellitus*. *Minerva Pediatr* 1995; **47**(6): 245-248.

[10] **Hopkins DF, Cotton SJ, Williams G.** Effective treatment of insulin-induced edema using ephedrine. *Diabetes Care* 1993; **16**(7): 1026-1028.

تقرير حالة: الاستسقاء المستحث بالإنسولين في فتاة عمرها ١٣ عاما

عبد المعين الأغا ، و علي رشيد أوكلتري

قسم الأطفال، كلية طب، جامعة الملك عبدالعزيز

جدة – المملكة العربية السعودية

المستخلص. فتاة عمرها ١٣ عامًا تعاني من داء السكري من النوع الأول لمدة سبع سنوات وبسيطرة ضعيفة على المرض، قدمت الاستسقاء الجسم مع زيادة سريعة في الوزن (٧ كلغ في ١٠ أيام). تطورت الاستسقاء بعد أسبوع من بدء علاج الأنسولين المكثف. ولقد بدات الاستسقاء بأطراف الفتاة السفلية. بعد إجراء التحاليل تم استبعاد الأسباب الأخرى التي يمكن أن تسبب الاستسقاء. مع الاتجاهات الراهنة تجاه العلاج بالأنسولين المكثف، ينبغي للأطباء أن يكونوا على بينة من وجود متلازمة الاستسقاء الأنسولين. وينبغي توثيق حدوثه وتمييزه عن الأسباب الأخرى المسببة للاستسقاء.