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Insulin Induced Edema in a Patient with Type 3c (Pancreatogenic) Diabetes

Dr. Jacob Neil (MD)[1*], Dr. Asha Anne Jacob (MS)[2]
[1]Specialist Internal Medicine, Dept. of Internal Medicine, WellKins Medical Centre Doha, Qatar
[2]Specialist Ophthalmologist, Dept. of Ophthalmology, WellKins Medical Centre Doha, Qatar

Abstract: Insulin edema is a rare complication of insulin therapy that can occur after the initiation and intensification of insulin commonly seen in Type 1 Diabetes with chronic hyperglycemia. Here, we report the occurrence of generalized edema in a 24-year-old man with Type 3 c (Pancreatogenic) diabetes due to chronic pancreatitis, early after the initiation and self- intensification of insulin. Various differentials were excluded, and resolution of edema was achieved after 3 weeks with diuretics. The incidence of Insulin edema being a rare occurrenceand as a diagnosis of exclusion we present this case to increase awareness as it carries a goodprognosis. We reviewed the current literature and the possible mechanisms behind this phenomenon.

Keywords: Diabetes, pancreatogenic, edema, insulin.

Review Paper

***Corresponding Author:**
Dr. Jacob Neil
Specialist Internal Medicine, Dept. of Internal Medicine, WellKins Medical Centre Doha, Qatar

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INTRODUCTION

Edema is a common sign observed in many patients in an outpatient setting. Peripheral or generalized edema is a rare complication of insulin therapy, that mostly occurs after initiating and intensifying insulin treatment in patients with newly diagnosed or poorly controlled diabetes [1, 2].

This report describes the occurrence of generalized edema in a 24-year-old man with type 3c Diabetes Mellitus (pancreatogenic diabetes) soon after the initiation and intensification of insulin therapy. Significant differential diagnoses were excluded, and resolution of edema was achieved after three weeks of diuretics therapy. We reviewed the current literature and the possible mechanisms underlying this phenomenon.

Narrative

A 24-year-old male of Indian origin presented with a history of diabetes mellitus for 7 years and past history of pancreatitis in 2013 with recurrent attacks in 2015, following which he was diagnosed with diabetes, who initially presented with complaints of weight loss, fatigue and inability to focus and was detected to have uncontrolled blood glucose levels. He was on treatment with Glucophage (Metformin) 2000 mg per day Amaryl (Glimepride) 2 mg per day and Trajenta (Linagliptin) 5 mg OD. After increasing up the dose of Amaryl to 4 mg Od (stepped up to a maximum dose of 8 mg) and Inj. Lantus (Glargine) 20 units at night his serum glucose remained high, Inj. Novorapid (Insulin Aspart) was started and the patient was advised to monitor the glucose levels and adjust the dosage if needed, Oral medications were stopped except for Metformin. Initially on Inj. NOVORAPID 10- 10-8 + Inj. Lantus 26 units at night. His blood glucose levels were brought down to normal levels, and he was monitoring and adjusting the dose by himself frequently upto Novorapid 36-32-36 units and Lantus 30 units. On 03/06/2023 he presented with pain in the lower limbs and swelling of the both the lower limbs which initially started in the ankle joints and progressed to the upper limbs and over 1 week to a generalized edema. Upon examination, he weighed 88kg; which was 8kgs more than his last measured weight. He appeared slightly dyspneic, with a respiratory rate of 20 breaths/min and oxygen saturation of 96% on ambient air. His pulse rate was 100 beats/min (regular), and blood pressure was 120/70 mmHg. His jugular venous pressure was not elevated when lying at 45 degrees. His first and second heart sounds were clearly audible, with no additional sounds. The patient had generalized pitting edema, which was more evident in the lower limbs. No visible varicose veins nor cutaneous changes were observed, and his edematous legs were neither hot nor tender on palpation. The breath sounds were normal to auscultation, with no audible crackles. The abdomen was soft to palpation, and there was no hepatosplenomegaly, no distension, shifting dullness, or abdominal guarding. The neurological examination

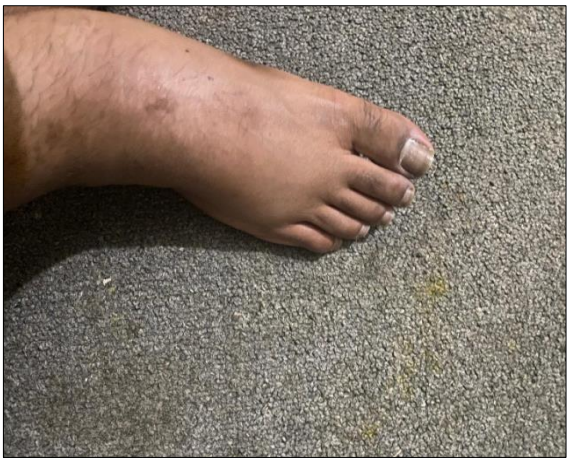
results were within normal limits. Fundus evaluation revealed no signs of diabetic retinopathy.

As the patient's main symptom were generalized body swelling, full laboratory investigations were performed along with ECG, X-ray chest, screening 2D echocardiogram and Duplex USS of the lower limb for venous insufficiency. The chest radiography revealed no evidence of congestive heart failure, cardiomegaly, or pericardial disease. No significant electrocardiographic changes were observed. Trans-thoracic echocardiography and Duplex ultrasonography of the lower limbs showed normal results. Urine Analysis was normal.

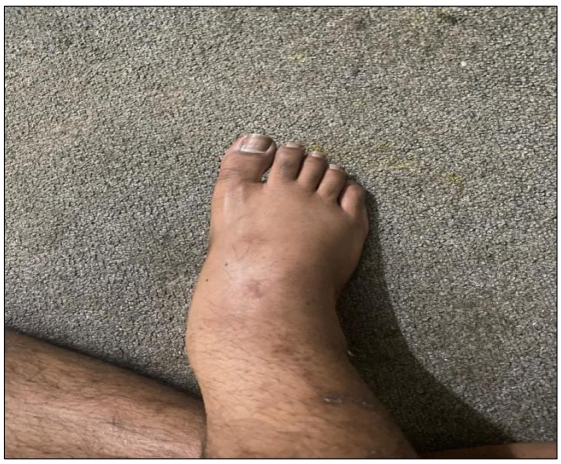
After ruling out the differentials for edema we concluded that edema maybe insulin induced edema and he was advised a salt restricted diet and to reduce the dose of insulin, the edema still persisted and he was started on loop diuretic furosemide for the edema but did not show any improvement after 1 week, aldosterone antagonist spironolactone was added and within 3 weeks, the edema subsided completely.

Diagnostics

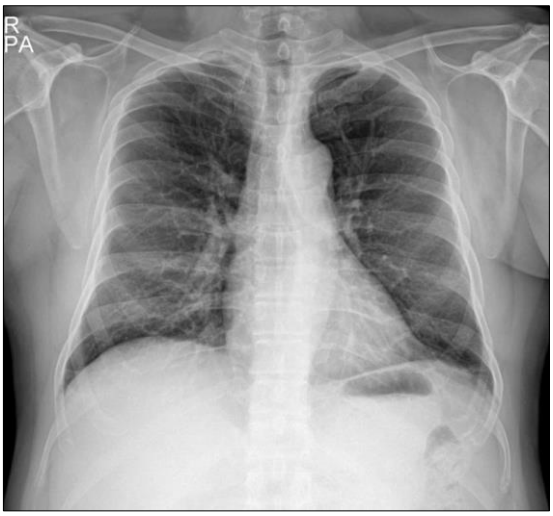
Type	Value	Unit
2023-02-02		
ALT (alanine aminotransferase)	19	IU/L
AST (aspartate aminotransferase)	14	IU/L
Hb (hemoglobin)	16.4	g/dL
2023-02-04		
Creatinine	0.65	mg/dL
FBS (fasting blood glucose)	262	mg/dL
HbA1C (hemoglobin A1C)	10	%
Uric acid	3.9	mg/dL
2023-02-06		
TSH (thyroid-stimulating hormone)	2.06	µU/mL
2023-04-06		
Cholesterol, total	176	mg/dL
Creatinine	0.7	mg/dL
Glucose	311	mg/dL
HbA1C (hemoglobin A1C)	8.9	%
2023-06-03		
Albumin	4.8	g/dL
ALT (alanine aminotransferase)	50	IU/L
AST (aspartate aminotransferase)	51	IU/L
BUN (blood urea nitrogen)	35	mg/dL
Creatinine	0.9	mg/dL
Glucose	62	mg/dL
2023-07-10		
25(OH)D (25-hydroxyvitamin D)	9.1	ng/mL
Glucose	92	mg/dL
HbA1C (hemoglobin A1C)	7	%



Picture 1: Lower limb edema



Picture 2: Lower limb Edema



Picture 3: Chest Xray done on Day 1 of presentation with edema

DISCUSSION

Insulin edema is defined as an edema syndrome that occurs in patients with either type 1 or type 2 diabetes after the introduction or intensification of insulin treatment. It is a transient and benign and usually a self-limiting condition that resolves spontaneously

without any treatment or with diuretic therapy; however, it can present in a variety of ways, ranging from mild peripheral edema to cardiac failure and massive serosal effusions [2-6].

Insulin edema is an underreported physical finding following the initiation and intensification of insulin therapy. The first case was reported in 1928 by Leifer in a middle- aged man who presented with diabetic ketoacidosis, and Shaper [7] in 1966 made a revision in Kampala (Africa), which found 3.5% of cases of registered diabetics between 1950 and 1961. Although minor insulin edema might be underrecognized, the incidence of notable or severe insulin edema seems to be a rare event [8]. The true incidence of insulin edema remains unknown; however, some reports have estimated it to be in the range of 3%-3.5% [6]. Clinical factors that can contribute to the development of insulin edema include poor glycemic control, new-onset diabetes, type 1 diabetes, low body weight, poor nutritional status, and higher doses of insulin therapy [8, 9]. Many reported cases of insulin edema have been in substantially malnourished or underweight individuals [8-10].

Our Patient with history of recurrent pancreatitis first episode in 2013 and repeated attacks in 2015 and history of Diabetes since 2015 we considered this patient to have Type 3c (Pancreatogenic) Diabetes secondary to chronic pancreatitis. Diabetes can also develop as a direct consequence of other diseases, including those of the exocrine pancreas. Historically, diabetes due to diseases of the exocrine pancreas has been described as pancreatogenic or pancreatogenous diabetes mellitus, but recent literature has referred to it as type 3c diabetes. It is important to note that type 3c diabetes is not a single entity; it occurs due to a variety of exocrine pancreatic diseases with varying mechanisms of hyperglycemia. The most commonly identified causes of type 3c diabetes are chronic pancreatitis, pancreatic ductal adenocarcinoma, haemochromatosis, cystic fibrosis, and a history of pancreatic surgery [11]. In our patient the main contributing factors to the edema were rapid intensification, higher Insulin dosing and occasional hypoglycemic episodes. We reviewed the various mechanisms that could have contributed to the development of edema.

Initially, Leifer proposed that rapid retention of tissue fluid secondary to glycogen deposition was responsible for the pathophysiology. Shaper added that the accumulation of lactic and pyruvic acids in the tissues with a relative deficiency of thiamine due to a high carbohydrate diet in the process of re-establishing metabolic balance in cachectic patients caused extreme vasodilatation of the peripheral blood vessels [7-13].

Several theories have been postulated regarding the pathophysiological mechanisms of insulin edema. These include the direct antinatriuretic effect of insulin on the renal tubules, increased glucocorticoid retention due to insulin-induced hypoglycemia, and increased vascular permeability [8]. Another possible mechanism is the loss of albumin due to transcapillary leakage [14]. Nevertheless, the peripheral oedema could have been caused by the rapid improvement in glycemic control, rather than the initiation of insulin therapy itself. Rapid improvement of blood glucose profile has been reported to be associated with reduced plasma osmolality that subsequently leads to intracellular water retention, i.e., oedema[14]. Rapid improvements in glycemic control have long been known to increase the risk of decompensating diabetic retinopathy [15]. Insulin is known to cause the reabsorption of sodium in the kidneys by stimulating the Na+/K+-ATPase as well as the expression of Na+/H+ exchanger 3 in the proximal tubule, and it also causes vasodilation, which contributes to fluid retention. Hyperglycemia also independently causes an increase in vascular permeability, which is consistent with the development of edema in patients with persistently elevated glucose levels (8). Persistently elevated glucose levels in diabetic patients cause poor integrity of the vascular membrane, which increases the risk of edema as a result of rapid changes in serum osmolarity. This proposed mechanism is supported by the phenomenon of "refeeding edema." Refeeding edema occurs with an increase in endogenous plasma insulin levels associated with carbohydrate ingestion after prolonged starvation [16].

Renal tubular sodium reabsorption is enhanced by insulin therapy via stimulation of the Na+/K+-ATPase and the expression of Na+/H+ exchanger 3 in the proximal tubule (17,18). It has been suggested that transient inappropriate hyperaldosteronism contributes to fluid retention [17].

Genetic susceptibility has also been postulated in this regard. Suzuki *et al*., reported four patients with insulin- induced oedema, all of whom had a 3243 mitochondrial tRNA mutation, in contrast with 197 patients without the mutation among whom, no case of insulin oedema was documented [19].

The reported weight gain in insulin-related oedema has ranged from 1.8 to 20kg [8-17]. Sometimes edema may gradually be replaced by fat tissue with persistent weight gain [20]. Treatment of insulin induced edema is with salt restriction, reduction in the dose of insulin with achievement of good glycemic control. Diuretics have been used in the treatment of insulin-induced edema [21], but their role has been controversial but mostly with good results in the majority of patients. Their use can be justified by the fact that insulin is a salt-retaining drug; however, clear evidence is lacking.

Some endocrinologists could justify the use of aldosterone antagonists, which is supported by the presence of transient hyperaldosteronism, although loop diuretics are usually sufficient. However, ephedrine

showed promising results in the treatment of insulin-induced edema. Despite being a vasoconstrictor and sympathomimetic agent, it may be superior to diuretic therapy in selected cases [22].

Based on the above observations our patient would have developed edema secondarily due to the antinatriuretic effect of insulin along with the rapid correction of the hyperglycemic state by intensifying his insulin dosage rapidly leading to few episodes of hypoglycemia as well as inappropriate hyperaldosteronism contributing to the edema. He developed edema approximately 7 weeks after initiation of insulin in a basal bolus regime and the dose was adjusted frequently by himself during these 7 weeks to very high doses approximately 104 units of Insulin Aspart per day (in divided doses) and 30 units of insulin glargine. Our patient had a weight gain of 8kgs which subsided with reduction in the insulin dose and with diuretics. The edema initially did not show any response with salt restriction and to furosemide but with the addition of spironolactone the edema subsided completely.

Patient Perspective

The patient presented with uncontrolled glucose levels for which he had been struggling for almost 2 years on oral medications but did not show any control of his glucose. His medications were stepped up to observe the response but did not show any improvement, and he showed a good response after changing to a basal bolus regimen. However, frequent increases in the dose of rapid acting insulin alone led to a few episodes of hypoglycemia. He developed swelling in both feet, and then followed by his hands and then facial edema as well.

CONCLUSION

Insulin edema syndrome is a rare, underreported complication of insulin therapy. Patients who present with edema and have been recently started on Insulin should have this clinical entity as an element in their differential diagnoses. This is commonly observed in patients with Type 1 and Type 2 diabetes who have been initiated on insulin. After excluding other cardiac, hepatic, vascular, and nephrotic causes of sudden onset edema, it is reasonable to attribute the etiology to this under-recognized phenomenon. Awareness of this condition will reassure patients and enable them to adhere to their insulin regimen. Insulin induced edema is usually treated with salt restriction and insulin dose reduction as needed and if persistent, the addition of loop diuretics can be considered. If no response is seen with loop diuretic addition of an aldosterone antagonist, it would be beneficial in view of the transient hyperaldosteronism state and if unresponsive to these medications' ephedrine may be considered.

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Patient Permission/Consent Declarations

Written informed consent was obtained from the patient for including his anonymous information in this clinical case report.

Department and Institution Where Work Was Done:

Department of Internal Medicine, Wellkins Medical Centre, Doha Qatar

Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the committee responsible on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

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