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Insulin Edema in Newly Diagnosed Type 1 Diabetes Patient

Yeni Tanı Tip 1 Diyabetli Hastada İnsülin Ödemi

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Abstract

Insulin edema is a rare complication seen in patients with newly diagnosed, poorly controlled diabetes in a short period of time after starting intensive insulin therapy. It frequently limits itself. In this case report, we present an underweight patient with newly diagnosed type 1 diabetes mellitus who presented with diabetic ketosis and developed insulin edema following hydration and high-dose insulin therapy.
Keywords: Adolescent, insulin-induced edema, newly diagnosed type 1 diabetes

Öz

İnsülin ödemi, sıklıkla yeni tanı ve kötü kontrollü diyabetlilerde yoğun insülin tedavisi başlandıktan kısa bir süre sonra ortaya çıkan nadir bir komplikasyondur. Sıklıkla kendi kendini sınırlar. Bu bildiride biz, diyabetik ketozisle prezente olan, yeni tanı tip 1 diyabetli, zayıf bir hastada yüksek doz insülin tedavisi ve hidrasyon sonrası insülin ödemi gelişen bir olguyu sunduk.
Anahtar kelimeler: Adölesan, insülin indüklenmiş ödemi, yeni tanı tip 1 diyabet

Introduction

Insulin plays an essential role in the treatment of diabetes mellitus (DM). The most frequent side effects of insulin therapy are hypoglycemia and weight gain. However, insulin edema can also develop in relation with insulin therapy, though this complication is rare. It is often observed in patients with newly diagnosed type 1 DM or poorly controlled type 2 DM following intensive insulin therapy or following a high-dose insulin therapy among underweight diabetics (1). Insulin edema is probably an underdiagnosed phenomenon; therefore, its true incidence rate is not known. It is reported most often among children and adolescents (2). Despite its self-limiting nature, it is rarely observed with pleural effusion, heart failure, or generalized edema (3). In this case report, we aimed to draw attention to the edema developing after high-dose insulin therapy and overhydration in an underweight patient with newly diagnosed type 1 DM who presented with diabetic ketosis.

Case Report

An 18-year-old male patient was admitted to the hospital with a one-month history of excessive water consumption, pollakiuria, polyuria, and 6 kg weight loss. Physical examination at the time of admission revealed a temperature of 36.2 °C, a pulse rate of 95 beats per minute, a respiratory rate of 16 per minute, and a blood pressure of 110/70 mm/Hg. His height was 165 cm, his weight was 49 kg, and his body mass index was 18 kg/m^2. Laboratory examination showed hyperglycemia (fasting blood glucose 322 mg/dL) and ketonuria and arterial blood pH of 7.38, and A1c level of 16.7% (Table 1).

The patient was hospitalized in the endocrinology clinic with the diagnosis of type 1 DM with ketosis. He was initially treated with an intravenous infusion of insulin and isotonic saline for hyperglycemia and ketonuria. After clinical improvement, basal-bolus therapy was begun. At the follow-up visits, his insulin requirement increased to approximately 2U/kg/day (morning, noon, evening, with 20 units of insulin aspart, and 40 units of insulin detemir at night).

Fifteen days after discharge, the patient was again admitted to the clinic with swelling in both legs. His temperature was 36.5 °C, he had a heart rate of 82/minute, and his arterial blood pressure was 120/70 mm/Hg. The patient had pitting pretibial and ankle edema in both extremities (Figures 1 and 2). The respiratory system and cardiovascular system examinations were normal. In the laboratory examination, hyperglycemia (fasting blood glucose: 211 mg/dL) and mild hypoalbuminemia (3.5 g/dL) were detected; other biochemical blood test results were normal (Table 1). The patient was hospitalized again. No proteinuria was detected in his urine. Chest x-ray, echocardiography, and abdominal and lower extremity Doppler ultrasonography results were also normal.

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Thus, other factors that could have caused the edema were ruled out. Basal-bolus therapy was continued. At follow-up visits, the patient's need for insulin was seen to decline (1.5 U/kg/day). With reduced insulin doses, the edema regressed spontaneously. The patient is still on follow-up with basal-bolus therapy.

Discussion

Edema is a rare complication of insulin therapy. First defined by Leifer (4), its severity spans a wide spectrum, from ankle edema to generalized edema accompanied by acid and pleural effusion (5). The cause and the incidence of insulin edema are not clearly defined, and diagnosis can be made only by excluding other causes of edema. While insulin edema is observed at similar rates in both genders, it is observed most frequently among younger female patients (6). Moreover, interestingly, the majority of insulin edema cases reported in the literature have occurred in underweight individuals. The case we present here was also an underweight adolescent, similar to others described in the literature. However, the patient was male and had limited pitting edema in the lower extremities.

Insulin edema occurs almost always shortly after the initiation of intensive insulin therapy in newly diagnosed and poorly controlled diabetics (2). Local or systemic edema can develop in patients with uncontrolled diabetes when their blood glucose level falls rapidly. For instance, Baş et al. (7) have reported two patients with newly diagnosed type 1 DM who presented with edema of the lower extremities nearly one week after initiation of insulin treatment. Spontaneous recovery was observed in both patients. Mamoulakis et al. (1) described a patient with newly diagnosed type 1 DM who presented with periorbital edema and edema of the lower extremities one day after beginning insulin treatment. After the exclusion of other causes of edema, furosemide was started, and the edema was resolved within ten days. Evans et al. (3) reported a 35-year-old markedly underweight woman with uncontrolled diabetes who presented with extensive peripheral edema, bilateral pleural effusions, and a weight gain of 18.8 kg in 22 days following insulin therapy. She responded well to treatment with diuretics, losing 10.3 kg in six days.

Table 1. Biochemical parameters of the case

Parameters	At diagnosis time	Fifteen days after discharge	Normal range
Blood tests Glucose, mg/dL	 322	 211	 74-106
BUN, mg/dL	15	12	6-20
Creatine, mg/dL	0.4	0.4	0.2-1.3
Albumin, g/dL	4.0	3.5	3.5-5.5
ALT, IU/L	22	20	7-45
Calsium, mg/dL	8.7	8.9	8.6-10
Sodium, mEq/L	135	136	136-145
Potassium, mEq/L	4.2	4.5	3.5-5.5
A1C, % C peptide, ng/Ml TSH Ketonuria	16.7 0.2 1.2 +3 positive	- - 1.5 Negative	4-5.6 0.9-4.3 0.4-4.2 mIU/L
Arteriel blood gas			
pH	7.38	7.40	7.35-7.45
HCO_3, mmol/L	18	22	22-26
PCO_2, mmHg	40.5	38	35-45
PO_2, mmHg	95.2	92	80-100
Microalbuminuria mg/day	15	10	<30

ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, HCO_3: Bicarbonate, PO_2: Partial oxygen pressure, PCO_2: Partial carbon dioxide pressure, TSH: Thyroid stimulating hormone

The exact cause of this condition is not known. In the case of a catabolic state due to lack of insulin, intensive fluid therapy may lead to liquid extravasation in subcutaneous tissue which may result in peripheral edema. This condition can also worsen due to increased capillary permeability caused by chronic hyperglycemia (8). The case presented here was in a catabolic state. It was presumed that the peripheral edema had been caused by both a chronic hyperglycemia-related increase in capillary permeability and liquid extravasation in the subcutaneous region following intensive fluid therapy. Insulin has been recognized to have a direct anti-natriuretic effect on the kidney (9). Insulin therapy increases renal tubular sodium reabsorption by stimulating Na,K-ATPase in the proximal tubule (10). Temporary inappropriate hyperaldosteronism can also contribute to fluid retention (11). Insulin has been proven to increase vascular permeability in both healthy individuals and diabetics (12). Loss of albumin from circulation due to increased transcapillary leakage is likely to contribute to edema formation as well (13). However, there have been reports of cases of edema with normal albumin levels (6). The case we present here had mild hypoalbuminemia (3.5 g/L), most probably due to increased transcapillary leakage. Additionally, in diabetic patients, who have volume loss and are malnourished, an increased need for insulin can lead to edema formation by reducing renal excretion and increasing free water retention (14). Our case was an underweight, newly diagnosed adolescent type 1 DM patient with insulin deficiency who developed peripheral edema ten days after the initiation of insulin therapy.

Another possible cause is thiamine deficiency, according to Shaper (15) has been claimed to cause acute water retention. This condition can lead to edema by causing the over-dilation

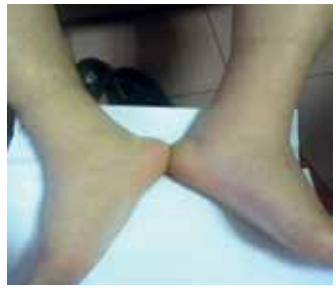

Figure 1. Pitting edema in bilateral lower extremity

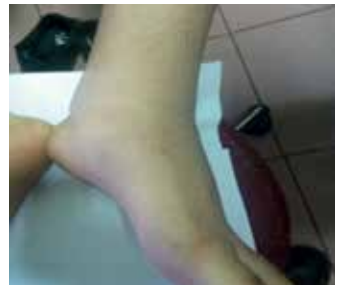

Figure 2. Edema in left ankle

of peripheral blood vessels due to the accumulation of lactic acid and pyruvic acid in tissue and blood fluids. In the process of rebuilding metabolic balance in cachectic diabetic patients, a high-carbohydrate diet can lead to a relative thiamine deficiency and, consequently, edema formation. We could not evaluate thiamine levels in our case.

Another possible mechanism of edema formation in our case was overhydration. Various hormones, such as antidiuretic hormone, glucagon, and aldosterone, play a role in edema formation after rehydration. High antidiuretic hormone levels during chronic hyperglycemia and insufficient water excretion during fluid replacement can cause fluid retention. Poor glycemic control is associated with increased glucagon levels, and increased glucagon inhibits the effects of aldosterone in circulation. Therefore, a rapid achievement of glycemic control leads to a reduced concentration of glucagon in the blood and the subsequent elimination of the inhibitory effects on aldosterone, causing water retention. Moreover, insulin-related hypoglycemia can also cause water retention due to the known effects of contra-regulatory hormones (i.e., glucocorticoids and glucagon) on renal sodium and free water excretion (16). In their study in 2003, Khalangot et al. (17) investigated the incidence of insulin edema in diabetic patients receiving treatment for ketoacidosis showed that after treatment, 17% (n=13) of patients had insulin edema. This finding supports that overhydration may be a possible mechanism for insulin edema. Our case had also ketosis and was treated with hydration and insulin.

Insulin edema often improves spontaneously in seven to 20 days, and decreased insulin doses can also help to reduce edema (18). The edema in our case regressed in seven days, following a relative decline in insulin dose as well. Short-term diuretic treatment (1), salt restriction, and ephedrine (6) may be effective in the treatment of acute edema. There are reports of the use of combined ephedrine and diuretic therapies in the literature (19).

In this report, there are several limitations. Although plasma antidiuretic hormone , renin, and aldosterone levels should be evaluated in insulin edema, we could not assess these hormone levels. Furthermore, thiamine deficiency is also a cause of edema, but the thiamine levels could not be evaluated in this case.

Conclusion

In conclusion, insulin-induced edema is not adequately recognized. More importantly, most cases have a mild course and improve spontaneously, resulting in underreporting. The possibility of the development of insulin edema should always be considered when initiating intensive insulin and fluid therapies in newly diagnosed, malnourished, and underweight diabetic patients, especially in those with ktoacidosis. Therefore, we believe that intensive insulin and fluid therapy should be considered in the differential diagnosis of edema in these patients.

Ethics

Informed Consent: It was taken.
Peer-Review: Externally peer-reviewed.

Authorship Contributions

Concept: Ayten Oğuz, Design: Ayten Oğuz, Dilek Tüzün, Data Collection or Processing: Ayten Oğuz, Dilek Tüzün, Murat Şahin, Didem Atay, Berivan Ganidağlı, Kamile Gül, Analysis or Interpretation: Ayten Oğuz, Dilek Tüzün, Murat Şahin, Didem Atay, Berivan Ganidağlı, Kamile Gül, Literature Search: Ayten Oğuz, Dilek Tüzün, Murat Şahin, Didem Atay, Berivan Ganidağlı, Kamile Gül, Writing: Ayten Oğuz.

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