

PERIPHERAL INSULIN EDEMA AND PERICARDIAL EFFUSION IN A 12-YEAR-OLD NEWLY DIAGNOSED GIRL WITH TYPE 1 DIABETES

Aleksandra Janchevska^{1,2}, Valentina Jovanovska^{1,2}, Olivera Jordanova^{1,2},
Ardiana Beqiri-Jashari^{1,2}, Marina Krstevska-Konstantinova^{1,2}, Velibor Tasic^{1,2}, Zoran S. Gucev^{1,2}

¹ University Children's Hospital, Skopje, RN Macedonia

² Medical Faculty, Skopje, RN Macedonia

Corresponding author: Aleksandra Janchevska, MD, PhD, Assistant Professor, Department of endocrinology and genetics, University Children's Hospital, Medical Faculty, Mother Teresa 17, 1000 Skopje, North Macedonia, Email: dr.sasha1969@yahoo.com

ABSTRACT

Introduction: Insulin induced edema (IIE) is a rare condition, usually found in newly diagnosed diabetes patients, either after insulin treatment initiation or after dose increment. It is a self-limited process, rarely associated with serosal effusions. Teenage girls with type 1 diabetes (T1DM) are most commonly affected.

Patient and Methods: A 12-year-old girl was diagnosed with ketoacidosis (DKA). Seven days after initiation of the insulin treatment, at a stable total daily dose of insulin (TDDI) of 0.55 IU/kg, she came with two kilograms weight gain in only two days and edema of the feet and calves. Ultrasound of the heart found a 7 mm pericardial effusion. The diagnostic workout included clinical examination, biochemical, hormonal, allergen analyses and imaging which excluded other known causes of swelling.

Conclusions: We describe an adolescent girl with newly diagnosed T1DM and a rare association of peripheral insulin-induced edema and pericardial effusion. Short-term diuretic treatment and salt restriction resolved this rare complication of insulin treatment.

Keywords: insulin induced edema, diabetes mellitus type 1, adolescent girl, pericardial effusion

INTRODUCTION

Insulin Dependent Diabetes mellitus (Type 1 DM) is the most common metabolic disorder in childhood and adolescence [1]. T1DM results in acute and chronic complications. The most frequent acute complications are hypoglycemia and diabetic ketoacidosis (DKA). There are numerous other known, but rare complications and associated conditions [1, 2]. Insulin-induced edema (IIE) is an extremely rare complication [2]. Adolescent girls with T1DM are most frequently affected [3]. However, older patients with T2DM have also been reported.

PATIENT AND METHODS

A 12-year-old girl (BMI=19.4, BMI z-score=0.52) with weight loss, fatigue and polyuria was diagnosed with moderate ketoacidosis (DKA) (ph=7.19, HCO₃⁻=9.4 mmol/l, BE= -24.7 mmol/l, pCO₂=9.0 mmHg). There were elevated glycosylated hemoglobin (HbA1c) at 11.6% and decreased insulin (< 2 uIU/ml) and C-peptide (0.615 ng/ml) serum concentrations. The diabetes antibodies were elevated (ICA=55.05, N <28 E/ml, IA-2 >280.0, N <28 E/ml). The DKA was resolved in two days, and the girl started a basal-bolus regimen with insulin Aspart and



Fig. 1a and Fig. 1b. *Panel peripheral insulin-induced edema*

Deglutec. She had a stable total daily dose of insulin (TDDI) 0.55 IU/kg. A week later, the girl returned with a 2kg weight gain (BMI=22.2; BMI z-score=1.21) and edema of the feet [Fig. 1a]. The renal, hepatic, thyroid, rheumatic causes of edema were excluded. There was not personal or family history of allergy, while a nutritional and inhaled antigens test was uneventful. Viral serology (adeno, cytomegalovirus, influenza, parainfluenza, respiratory syncytial virus and Covid 19) was uneventful. The electrocardiogram and chest radiography were normal, while the ultrasound of the heart revealed a 7 mm pericardial effusion, with ejection fraction of 60% and with normal ventricular function motions. Within 10 days of furosemide treatment and a low-salt diet, the edema of the feet and calf disappeared [Fig. 1b] and the heart ultrasound revealed a complete resolution of the pericardial effusion.

DISCUSSION

In 1928, Leifer described the first patient with IIE in a 41-year-old man with diabetes [4]. Fifty years later, in 1979, this condition without serous effusion was reported in a 12-year-old boy with T1DM [5]. So far, at least 23 children and adolescents under 18 years with T1DM and insulin-induced edema have been reported [3, 6].

Girls were more frequently affected (70%) [3]. In contrast, there is no gender or age preference for IIE among adults with T2DM.

The types of insulin or insulin treatment have no influence in the occurrence of edema [3, 7]. IIE was reported in children receiving NPH and analogue insulins in any insulin type of treatment, including insulin pumps [7].

Glycosylated hemoglobin in children with newly diagnosed diabetes and insulin edema was found to be between 12% to 18%. Although poor metabolic control has been supposed to contribute for insulin edema occurrence, adolescents with HbA1c less than 8% are also reported [3].

The pathophysiology of IIE remains unclear. Insulin plays a major role in increasing sodium reabsorption in the renal proximal and distal tubules and the Henle loop. Insulin also increases vascular permeability and vasodilation. Thiamine deficiency or detected mitochondrial mutation DM-Mt3243 have been suggested as risk factors for the development of insulin edema [3, 8].

Severe associated conditions such as nephrotic syndrome, congestive heart failure, ascites and pleural effusions have been detected in adults with generalized insulin edema [8, 9]. The insulin edema in majority of diabetic children and adolescents has peripheral distribution, starting from the feet and ankles up to the knees and thighs. Only few pediatric patients had generalized insulin edema. To date, only one 14-year-old adolescent girl

with T1DM has been described with generalized insulin edema and pericardial effusion [6]. The IIE in most patients does not require medical treatment and disappears spontaneously. However, in severe edema, a short-term course with furosemide and salt restriction in the diet have had a positive effect in its complete resolution.

Our patient is the first pre-teenage T1DM patient with newly diagnosed T1DM in whom pericardial effusion accompanies IIE. Her glycosylated hemoglobin (11.6%) is lower than expected for most patients with IIE. The girl was on a basal-bolus regimen with a stable and relatively low TDDI of 0.55 IU/kg at the time of onset of the complications. Ten days of treatment with furosemide and low-salt diet has resulted in complete resolution of pericardial effusion and edema.

CONCLUSIONS

IEE is an extremely rare acute complication in children with T1DM. IEE should not be overlooked or confounded with other causes of edema. Girls with poor metabolic control are more likely to develop peripheral or generalized edema. The accompanying pericardial effusion is extremely rare. Most patients have the edema resolved without treatment. However, in severe edema and/or pericardial effusion, short-term treatment with a low-salt diet and loop diuretics is effective.

REFERENCES

1. Sperling MA. *Pediatric Endocrinology*. Second Edition Philadelphia: WB Saunders Company 2002;325-53.
2. Mahmud FH, Elbarbary NS, Fröhlich-Reiterer E, Holl RW, Kordonouri O, Knip M et al. ISPAD Clinical Practice Consensus Guidelines 2018: Other complications and associated conditions in children and adolescents with type 1 diabetes. *Pediatr Diabetes*. 2018; 19: 275–86.
3. Sawalha N, Geddie H. Insulin edema associated with newly diagnosed type 1 diabetes and high glycated hemoglobin: A Case and Review of the Pediatric Literature. *Can J Diabetes* 2021;45(6):571-574.
4. Leifer A. A case of insulin oedema. *JAMA* 1928;90:610–11.
5. Lawrence JR. Diabetic (insulin) oedema. *BMJ* 1979;2:445.
6. Moravej H, Karamizadeh Z, Nikfarjam F, Amoozgar H. Pericardial effusion in a teenaged type 1 diabetic patient after insulin therapy. *Iran J Pediatr* 2012, 22 (4); 570-571.
7. Vasigh M, Mohammady J, Hopkins R. Insulin edema with use of U-500 regular insulin in a hybrid closed-loop insulin pump. *Cureus* 2020 10; 12(10): e10886.
8. Chelliah A, Burge MR. Insulin edema in the twenty-first century: review of the existing literature. *J Investig Med* 2004;52(2):104–108.
9. Lee P, Kinsella J, Borkman M, Carter J. Bilateral pleural effusions, ascites, and facial and peripheral oedema in 19-year-old woman 2 weeks following commencement of insulin lispro and detemir--an unusual presentation of insulin oedema. *Diabet Med* 2007; 24(11):1282-5.

Резиме**ПЕРИФЕРНИ ИНСУЛИНСКИ ЕДЕМИ И ПЕРИКАРДЕН ИЗЛИВ
КАЈ 12-ГОДИШНО ДЕВОЈЧЕ СО НОВОДИЈАГНОСТИЦИРАН ДИЈАБЕТЕС ТИП 1**

Александра Јанчевска^{1,2}, Валентина Јовановска^{1,2},
Оливера Јорданова^{1,2}, Ардијана Беќири-Јашари^{1,2},
Марина Крстевска-Константинова^{1,2}, Велибор Тасиќ^{1,2}, Зоран Гучев^{1,2}

¹ Универзитетска клиника за детски болести, Скопје, РС Македонија

² Медицински факултет, Скопје, РС Македонија

Инсулин-индуцираните едеми се ретка состојба, најчесто детектирана кај новодијагностицирани пациенти со дијабет или веднаш по започнување со инсулинскиот третман или по зголемување на инсулинската доза. Тоа е самоограничувачки процес, ретко асоциран со серозни ефузии. Најчесто афектирани пациентки се тинејџерки со дијабетес мелитус тип 1 (Т1ДМ).

Дванаесетгодишна девојка беше дијагностицирана со дијабетична кетоацидоза (ДКА). Седум дена по започнување со инсулинскиот третман, на стабилна вкупна дневна доза на инсулин (ВДДИ) од 0,55 IU/kg, таа имаше пораст од 2 kg во тежина за само 2 дена и едеми на стапалата и на потколениците. Ехотомографијата на срцето покажа постоење 7 mm перикарден излив. Дијагнозата беше поставена со клинички преглед, биохемиски, хормонски и алерголошки анализи, како и имџинг-техники што ги исклучија другите причини за едеми.

Прикажуваме адолесцентка со новодијагностициран Т1ДМ и ретка асоцијација на периферни инсулин-индуцирани едеми и перикарден излив. Краткотрајниот третман со диуретик и рестрикација на сол ја разреши оваа ретка компликација од инсулинска терапија.

Клучни зборови: инсулин-индуцирани едеми, дијабетес мелитус тип 1, адолесцентка, перикарден излив