

CASE REPORT

Generalised insulin oedema after intensification of treatment with insulin analogues

Luigi Adamo, Mark Thaelke

Barnes Jewish Hospital/
Washington University in
St Louis, St Louis, Missouri,
USA

Correspondence to
Dr Luigi Adamo,
ladamo@dom.wustl.edu

SUMMARY

We report a case of generalised insulin oedema after intensification of treatment with genetically modified insulin. This is the first case of generalised oedema in response to treatment with insulin analogues in a patient not insulin naive.

BACKGROUND

Insulin oedema is a rare complication of insulin treatment characterised by the development of lower extremity oedema or, less frequently, generalised oedema after administration of insulin.^{1 2} Insulin oedema typically develops after initiation of the insulin therapy, but few cases of insulin oedema after intensification of insulin treatment have been reported earlier.^{1 3-5} While insulin treatment per se does not produce liver dysfunction, insulin oedema can be associated with alteration of serum liver function tests.⁶ While multiple potential mechanisms underlying insulin oedema have been proposed,^{1 7 8} the pathophysiological basis of insulin-mediated generalised oedema remains unknown. Importantly, the medical literature reports one case of generalised insulin oedema after initiation of the therapy with insulin analogues,⁹ but modifications in the dose of insulin analogues have never been associated with the development of insulin oedema before.

CASE PRESENTATION

A 20-year-old black woman reported to the emergency department of our hospital with abdominal pain and vomiting and was diagnosed with diabetic ketoacidosis. The patient had type 1 diabetes mellitus since age 2 and diabetic nephropathy with persistent proteinuria. Her medical history was otherwise unremarkable. Her home medications were Lantus 30U daily, Lispro Sliding Scale three times a day with meals and Lisinopril 10 mg daily. The patient had no allergies, family history was positive for diabetes, social history was unremarkable with no history of smoking, no ethanol intake and no history of illicit drugs use. She had no known drug allergies. The patient reported missing her daily dose of Lantus the night before admission and worsening abdominal pain throughout the day until presentation to the hospital. In the emergency department she was found to have blood sugar 574 mg/dl, anion gap 27 mmol/l, plasma bicarbonate of 11 mmol/l, β -hydroxybutyrate 6.6 mmol/l and ketones in the urine (qualitative measurement reported as 4+ on a scale from 0 to 4). She was administered 2 litre of normal saline and was

started on an insulin drip at 6 units/h. After about 3 h, her anion gap was down to 12 mmol/l and her blood sugar down to 235 mg/dl. Her insulin drip was discontinued and she was transferred to the medicine department where she was restarted on Lispro Sliding Scale and Lantus once a day. Upon interviewing, the patient reported that she was usually compliant with her daily Lantus. However, she admitted inconsistent compliance with regular glucose measurements and Lispro Sliding Scale as reflected by a glycated haemoglobin (HbA1c) of 18.8% at admission.

The patient's physical exam was unremarkable 48 h after her initial presentation; her blood chemistry showed a mild anaemia and was otherwise within normal limits, her urine analysis showed modest proteinuria with unremarkable urine sediment. She was therefore referred to the diabetes education service and discharged home on Lantus 30 U daily, Lispro 7 U three times a day with meals and Lisinopril 10 mg daily. Her weight at discharge was 51.4 kg with a body mass index (BMI) of 21.4.

The patient presented to a follow-up appointment 6 days after discharge, reporting compliance with the newly prescribed medical regimen but complaining of shortness of breath and weight gain that had progressively developed since the time of discharge. Her physical exam was notable for a weight gain of approximately 10 kg (body weight 61.2 kg) and generalised oedema with trace facial oedema, bilateral lung crackles, 1+ bilateral upper extremities pitting oedema and 4+ bilateral lower extremities pitting oedema. The patient was admitted to the medicine service for further evaluation.

INVESTIGATIONS

On admission, the patient's urine analysis and blood chemistry were found to be unchanged from the time of discharge a week before with the notable exception of a newly developed elevation in alkaline phosphatase, alanine transaminase (ALT) and aspartate aminotransferase (AST), respectively, at 227, 99 and 316 Units/l. Importantly, thyroid stimulating hormone was within normal limits, brain natriuretic peptide BNP was low at 76 pg/ml and C reactive protein (CRP) was normal. Acute hepatitis panel and acetaminophen plasma levels were within normal limits. A transthoracic echocardiogram showed normal systolic and diastolic functions; abdominal ultrasound showed liver of normal size with coarsened echo texture and an otherwise normal abdominal cavity. In light of these findings, the patient was diagnosed with insulin oedema.

To cite: Adamo L, Thaelke M. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-007037

DIFFERENTIAL DIAGNOSIS

Generalised oedema is typically secondary to cardiac, renal or hepatic disorders. The absence of abnormalities on the trans-thoracic ECG and the presence of a normal BNP argue against a cardiac origin of generalised oedema in this patient. The presence of elevated liver function tests suggests a possible involvement of the liver. However, the patient has no signs of hepatic synthetic dysfunction (normal albumin and coagulation) and no evidence of liver disease upon abdominal ultrasound, and therefore her oedema could not be considered secondary to cirrhosis. The absence of proteinuria together with a normal microscopic urine analysis and the presence of normal creatine and electrolytes argue against the presence of renal disorders that could cause generalised oedema like acute glomerulonephritis or nephritic syndrome. Generalised oedema can be observed during flares of autoimmune disorders like lupus.¹⁰ We did not measure antinuclear antibody or erythrocyte sedimentation rate and therefore a lupus flare cannot be formally ruled out. However, the fact that the CRP was within normal limits strongly argues against the presence of an acute inflammatory state and the patient was not found to have any of the typical signs and symptoms of lupus like photosensitivity, malar rash, serositis, arthritis, haematological abnormalities or neurological symptoms. In the absence of evidence supporting an organic cause of generalised oedema, medications should be reviewed to identify possible causative agents. At the time of discharge from the hospital after her initial hospitalisation the patient was not started on any new drugs, but her insulin regimen was adjusted and the patient likely started to be more compliant with her insulin therapy.

TREATMENT

The patient was aggressively diuresed with Furosemide IV¹¹ and discharged home the third day after admission with moderate lower extremity oedema.

OUTCOME AND FOLLOW-UP

In 5 days period postdischarge the patient was back to her original weight. Her alkaline phosphatase, ALT and AST levels had decreased to 206, 75 and 110 Units/l. At a follow-up appointment 1 month later, her alkaline phosphatase, ALT and AST levels were back to normal (see table 1). The patient decreased her dose of basal insulin to 5 units three times a day. This was increased back from 5 to 7 units three times a day with meals 6 months after admission. Interestingly, the patient developed lower extremity oedema in response to this change. She reported to the emergency department of our hospital and was prescribed 20 mg daily of furosemide for 2 weeks with complete resolution of her symptoms. Since then, the patient remained stable on the increased insulin dose and her latest HbA1c, 10 months after her initial presentation, was 8.3%.

DISCUSSION

Before the initial admission for diabetic ketoacidosis, the patient was on a regimen characterised by a basal dose of long-acting insulin analogue at bedtime and insulin sliding scale three times a day with meals. She was poorly compliant with it as shown by a markedly elevated HbA1c of 18.8%. The patient reported that her poor compliance was mainly because of the fact that she did not like to check her blood glucose multiple times a day to calculate her sliding scale dose. The transition to a basal-bolus regimen characterised by a fixed amount of short-acting insulin analogue three times a day before meals in addition to an unchanged basal dose of long-acting insulin analogue at bedtime resulted in a sharp increase in daily insulin assumption, this triggered the development of insulin-induced oedema.

This case suggests that intensification of treatment with insulin analogues can induce generalised oedema and that practitioners should be aware of this unusual but possible reaction when adjusting therapy with any type of the insulin. Besides its relevance as description of an unexpected treatment outcome, we think that this case has interesting implications in the context of

Table 1 Synopsis of critical lab values

	At D/C—postinitial DKA	6 days post D/C—readmission with oedema	8 days post D/C—second day postreadmission	15 days post D/C—fifth day postreadmission	45 days post D/C—35th days postreadmission
WBC (K/mm ³)	5.4	7.1	7.5	5.3	
RBC (K/mm ³)	3.72	3.87	3.54	3.79	
Hg (g/dl)	10.4	10.8	10.1	10.5	
Hct (%)	31.8	33.4	30.7	27.6	
MCV (fl)	85.4	86.3	86.7	84.9	
Na (mmol/l)	140	139	134	141	
K (mmol/l)	3.4	4	4	3.8	
Creatine (mg/dl)	0.74	0.58	0.72	0.84	
Plasma protein (g/dl)		7.7	6.7	7.9	7.8
Albumin (g/dl)		4	3.6	4.2	4.3
Bilirubin (mg/dl)		0.2	0.2	0.1	1
Alk phosp (Units/l)		227	185	206	100
AST (Units/l)		99	79	75	36
ALT (Units/l)		316	228	110	46
BNP (pg/ml)		76			
CRP (mg/l)			2		
Weight (kg)	51.4	61.2		52	

ALT, alanine transaminase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CRP, C reactive protein; D/C, discharge from hospital; DKA, diabetic ketoacidosis; HCT, haematopoietic cell transplantation; MCV, mean corpuscular volume; RBC, red blood cell count; WBC, white blood cell count.

the debate on the mechanistic basis of insulin-induced oedema. In fact, the edematous reaction to insulin analogues with a transient elevation in liver enzymes that we describe is consistent with some of the suggested mechanisms of insulin oedema, such as insulin-mediated sodium retention and insulin-mediated increase in glycogen storage.⁷ However, the absence of evidence of pericardial effusion or ascites, together with the rapid development of generalised oedema in the context of an otherwise healthy patient receiving appropriate insulin supplementation, argue against other previously suggested mechanisms of generalised insulin-induced oedema, like insulin-induced increase in vascular permeability⁷ and insulin-mediated alteration of the colloidal properties of cells.⁸

The fact that the patient developed some oedema when her insulin dose was minimally increased suggests that the patient has an idiopathic tendency to retain fluids in response to increases in insulin dose. The fact that the patient has a strong family history of type 1 diabetes but no history of insulin-induced oedema, suggests that the origin of her unusual response to insulin treatment might not be entirely of a genetic origin.

Learning points

- ▶ Generalised oedema is a possible side effect of the intensification of insulin treatment.
- ▶ Generalised oedema can develop after intensification of treatment with insulin analogues.
- ▶ Insulin oedema is a diagnosis of exclusion.
- ▶ Insulin-induced oedema responds well to diuretic therapy.
- ▶ Salt restriction can be advised as a measure to prevent and treat insulin-induced oedema.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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