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ORIGINAL ARTICLE

Metabolic acidosis as a complication of intravenous dextrose administration in a patient with insulinoma

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Abstract There are few cases published in literature in which the use of intravenous dextrose as treatment for an insulinoma resulted in a metabolic acidosis. This is due perhaps to the usual method of administration, which is usually at low concentrations, for limited periods or low volumes. We present the case of a woman with suspected insulinoma by laboratory findings in which an endogenous hyperinsulinism was observed. During hospitalization, the patient required a progressive increase of the glucose infusion to prevent severe hypoglycemia. Two days before surgery, the patient presented symptoms of malaise and muscle weakness and a metabolic acidosis with hypokalemia became apparent in the blood analysis. This metabolic imbalance was attributed to a long period of treatment with high volume of intravenous dextrose infusion. If large doses of dextrose are required in a patient with an insulinoma, then the possibility of a metabolic imbalance must be considered during the follow-up. When the suspicion of an insulinoma is high, and all the attempts of pre-operative localization fail, patients should be derived early to specialized centers with modern imaging techniques, so that surgery is not delayed, and this rare and threatening complication could be avoided.

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Introduction

The insulinoma, although is a rare neuroendocrine tumor (four cases per million inhabitants), is the most common cause of hyperinsulinemic hypoglycemia in adults [1–6].

The tumor is difficult to locate with conventional imaging techniques [7–10], so that it is often necessary to use ultra-sensitive imaging techniques such as Endoscopic Ultrasonography (EUS) (94% sensitivity and 95% specificity) or helicoidal CT that, together, can achieve a sensitivity of approximately 100% [7, 11, 12]. When the tumor is not found before surgery, the most effective method to locate the tumor is the intraoperative ultrasonography [13].

An intravenous glucose infusion is required to maintain normoglycemia until surgery is performed. Other treatments that may help maintaining normoglycemia are diazoxide, calcium antagonists, and somatostatin [7].

Case

A 36-year-old woman with no relevant medical history had, since several years, episodes of dizziness and cold sweats, which took place in situations of fasting or strenuous exercise, improving with the intake of food. None of these clinical episodes were accompanied with a capillary glucose determination before hospital admission.

During hospital admission hypoglycemias were revealed on several occasions. A fasting test was performed, showing an inappropriately high insulin and C peptide for the patient's blood glucose (glucose: 1.9 mmol/l, insulin:

Days	-40	- 38	- 36	- 30	- 25	-23	-22	- 20	-15	- 14	-10	-9	-8	-5	-2	-1	0	+1	+2	+10
Comments	Day of admission				Diazoxide 300 mg/d Somatostatin 400 mg/d	Diazoxide cessation	Admssion in our hospital		Progressively Somatostatin dose reduction		Somatostatin cessation				*	*	Surgery	Saline 0,9%	Saline 0,9%	
Dextrose infusion	20% 60 ml/h	20 % 70 ml/h	20 % 80 ml/h	20 % 100 ml/h	20% 100 ml/h	20% 100 ml/h	30% 100 ml/h	30 % 100 ml/h	30% 120 ml/h	40 % 100 ml/h	40% 125 ml/h	40 % 125 ml/h	40 % 125 ml/h	40 % 125 ml/h	40 % 125 ml/h	40 % 125 ml/h	40% 125 ml/h	-	-	-
Basal Glycemia (mmol/L)	3.9	3.6	4.1	3.4	4.2	3.4	3.2	4.5	3.6	3.6	3.9	6.7	6.9	6.1	6.3		6.1	4.7	4.6	4.7
AST (UI/L)	20	22		58	60		55	57	50		55	50	55	30	33	40		45	42	20
ALT (UI/L)	12	12		60	80		75	70	77		75	75	70	73	70	73		40	39	16
TG (mmol/L)	0,90	0,82		1,13	1,46		1,40	1,94	2,35		2,98	2,92		2,75						1,04
pH	7,44				7,41						7,35			7,34	7,04	7,20	7,29	7,36	7,44	7,43
K (mmol/L)	4,3	4,2		4,3	4,1		4	3,9	3,7		3,7	3,5		3,3	1,8	2,2	3,3	4,3	4,4	4,3
Lactate (mmol/L)	1,26														7	9	10,3	5	1,5	

Fig. 1 Fluids, medications, and analysis throughout the course of admission. * During these 2 days was also administered: Intravenous potassium 120 mEq/day and Bicarbonate 1 Molar 500 mg/day

48.1 mU/l, C peptide: 3.60 ng/ml Cortisol: 15.3 mcg/100 ml, ACTH: 30.3 pg/ml). Sulfonylureas in urine were negative.

With the probable diagnosis of an insulinoma, an abdominal CT was performed which resulted negative. It was difficult to maintain normoglycemia despite intravenous infusion of 20% dextrose; therefore, the 15th day of admission, diazoxide (300 mg/day) and somatostatin (400 mg/day) were added to the treatment, without revealing any clear benefit in the patient's symptomatology. Before somatostatin use, an abdominal ultrasound was done without relevant findings. After 3 days since the initiation of diazoxide, the treatment had to be discontinued because of intolerance.

After 3 weeks of income, the patient was transferred to our hospital and admitted in our department, as we have more experience dealing insulinomas. An Octreoscan was performed, which did not show any positive uptake. An endoscopic ultrasound (EUS) displayed no relevant findings. Finally, a pancreatic multidetector CT revealed a hypodense, poorly demarcated lesion between the neck and body of the pancreas, of approximately 1 cm in diameter.

During this period of time, blood glucose became progressively more difficult to rectify, so dextrose infusion was increased from 20% concentration to 40% at a rate of 125 ml/h during the last week before surgery. Dose of somatostatin was gradually reduced and finally withdrawn on the 30th day of admission, because octreoscan had not shown evidence of somatostatin receptor expression.

The 38th day of admission, 2 days before surgery, the patient presented general discomfort and abdominal pain located at right upper quadrant, with no other signs or symptoms suggesting infection. The analysis evidenced hypokalemia and metabolic acidosis with increased lactic acid, there were no elevated markers of infection in the blood analysis (CRP low) [(Blood glucose: 6.3 mmol/l (4.2–6.1), Urea: 2.5 mmol/l (2.5–7.1), Creatinine: 79.5 µmol/l (53–106), Na: 136 mmol/l (133–146), K: 1.8 mmol/l (3.5–5.0), Amylase: 190 U/l (0–125), AST: 40 U/l (0–40), ALT: 73 U/l (0–40), total bilirubin: 6.8 µmol/l (5.1–22), total cholesterol: 5.40 mmol/l (1.30–6.09), LDL cholesterol: 3.28 mmol/l (<3.85), VLDL cholesterol: 1.08 (0.13–1.04), triglycerides: 2.75 mmol/l (0.56–1.51), Apo B: 2.3 [1, 2, 4], CRP: 8.6 mg/l (0–9), fibrinogen: 3.1 g/l (2.3–4.9), WBC: 18500/mcl (5–11000), Neutrophils: 68.5% (10–70), Hemoglobin: 119 g/l (120–158), Hematocrit: 37% (37–54), pH: 7.04 (7.33–7.42), HCO_3: 5.8 mmol/l (20–26), Lactic acid: 7 mmol/l (0.5–1.6))]. Blood and urine cultures were negative. A chest and abdominal x-ray were performed which showed no relevant findings. An abdominal ultrasound reported mild signs of fatty liver, with no other findings. The gallbladder examined with the ultrasound was normal. The patient was transferred to the ICU where the values were normalized with the use of intravenous potassium (120 mEq/day) and bicarbonate (Bicarbonate 1 Molar 500 mg/day). Dextrose infusion was not reduced. The 40th day potassium, HCO_3, and pH were normalized, and the surgery was performed. In the macroscopical study, a fatty liver was described.

After the surgery fluids and drugs could be withdrawn, maintaining the patient normal levels of glycemia. In the analysis of the 42th day of admission, the levels of lactate were 1.5 mmol/l. The patient was discharged with clinical stability and unaltered electrolytes or acid–base imbalance (see Fig. 1).

Discussion

In our case, the patient suffered an episode of lactic acidosis and hypokalemia after having received an increasing

dose of intravenous glucose administered during 5 weeks. Likewise, the nature of the illness had caused the patient to be exposed to large amounts of insulin. The exclusion of other causes of acidosis (no drugs were introduced that explained the increase in lactic acid, there were no impairment of kidney or cardiovascular function, there was not fever or elevated markers of inflammation) and hypokalemia suggests that the lactic acidosis in this patient may be related to the joint action of insulin and glucose. Another cause of lactic acidosis like a pyruvate dehydrogenase (PDH) deficiency was ruled out because the patient had no family members affected with congenital neurological problems. The thesis that suggests that the lactic acidosis is related to the action of insulin and glucose is reinforced by the fact that both metabolic impairments were corrected and remained stable without any medication once the glucose infusion was withdrawn and the insulinoma resected.

It is known that insulin can lower the levels of blood potassium by promoting its movement inside the cell [14], in fact, the administration of insulin and glucose is the standard treatment used for hyperkalemia [15].

Regarding the acidosis, it is unusually related to an intravenous glucose intake. Lactate can increase either by excessive synthesis from pyruvate, or by decreased metabolism in the liver or kidneys. Pyruvate is produced by glycolysis and, under normal aerobic conditions, is metabolized into acetyl-CoA (Pyruvate + CoA + NAD^+ = acetyl-CoA + NADH + H + CO_2) entering the mitochondrial Krebs cycle to produce energy in the form of ATP. The enzyme that catalyzes the step of pyruvate to Acetyl-CoA is the PDH. Under anaerobic conditions, lactic acid is produced in the cytoplasm of cells from pyruvate, due to an increased NADH production by hypoxia (pyruvate + NADH + H = Lactate + NAD) [16, 17]. In this case, however, anaerobic conditions did not exist, so that lactic acid production can not be explained by a phenomenon of tissue hypoxia. On the other hand, lactic acid can be metabolized in the liver to produce glucose, entering the pathway of gluconeogenesis, in the so-called Cori cycle [18]. Keeping this in mind, one might infer that an excessive increase of glycolysis, due to an excessive carbohydrate and insulin intake, could produce an excess of pyruvate that could not be oxidized at the mitochondria, resulting therefore in a synthesis of lactate. This could be due to saturation of PDH and to a depletion of NAD.

Reviewing the literature, other alternative hypotheses can be found. Winocur [19] and Jolliet [20] reported two similar cases, in which lactic acidosis was related to an increase of blood insulin and large doses of dextrose infusion. In both cases, it was concluded that lactic acidosis was secondary to a fatty liver caused by excess supply of glucose and insulin (endogenous in the first case, and exogenous in the second).

In this report, there was also a fatty liver, accompanied by a slight increase of liver enzymes. The liver steatosis can be explained by the increase of liver triacylglycerol due to an excess of carbohydrate and an increased insulin/glucagon ratio, which stimulates the path of de novo lipogenesis from acetyl-CoA [20, 21]. This increase of triglycerides is greater than the synthesis of Apo B-100 required for the transport of triglycerides as VLDL. Consequently, the excess of triglycerides is accumulated in the liver. Although, in fact, both de novo lipogenesis and protein synthesis of Apo B-100 are stimulated by insulin, it has been shown in animal and human studies that the regulation of lipogenesis may exceed that of the synthesis of Apo B-100 [20, 22, 23].

On the other hand, the phenomenon of lactic acidosis secondary to liver steatosis is unclear. An abnormality in the functioning of mitochondria could cause a failure of the pyruvate oxidation pathway, leading to an accumulation of it in the cell and, therefore, an increased synthesis of lactate.

This mechanism occurs in other situations not involved in this report. For example, there are many studies showing steatosis and lactic acidosis as a side effect of antiretrovirals by mitochondrial damage [24]. Also, in some studies of liver tumors, it was found that a mutation of the mitochondrial hexokinase, that is not properly inhibited by glucose-6-phosphate, may produce, in presence of carbohydrates, an increase of aerobic glycolysis and an excess of pyruvate that, unable to be oxidized in mitochondria, is diverted to the synthesis of cytoplasmic lactic acid [25].

Finally, another theoretical possibility might be that, as Jolliet et al. concluded in their case, a disturbance of the liver function secondary to fatty liver, could cause a decrease of the liver metabolism of lactate to the synthesis of glucose (Cori cycle), leading to an accumulation of lactic acid.

In this case, however, lactic acidosis can not be attributed only to a hypothetical mitochondrial or liver disorder due to liver steatosis, because lactic acidosis is not a common component of steatosis in other situations, such as non-alcoholic fatty liver, for example.

Conclusion

The hypothetical mechanisms that could have contributed to the lactic acidosis in our case are: (1) the excess of carbohydrate and insulin intake could have led to an increased glycolysis, producing an excess of pyruvate that, unable to be metabolized by the mitochondrial pathway

due to a saturation of the PDH or a depletion of NAD, could have result towards the synthesis of lactate, (2) a mitochondrial failure could cause an alteration of the Krebs cycle pathway, producing a pyruvate accumulation and, secondary, a lactate increase, and (3) a decrease of lactic catabolism by a failure of liver function secondary to hepatic steatosis could also cause a lactate increase.

It is more likely to support the first theory, although it is proper to have in consideration and discuss the other two as they have been reported in literature. The biggest drawback that we see in these last two theories is that in other pathologies with fatty liver (like non-alcoholic fatty liver) it is not a common finding. Anyway, the case alerts us that when the suspicion of insulinoma is high, and the preoperative localization of the tumor is unclear, the patient must be transferred early to specialized centers with ultrasensitive imaging techniques to locate the tumor, so that the surgical procedure is not delayed, especially in patients that, like ours, require large doses of intravenous dextrose.

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