CASE REPORT

Poorly controlled type 2 diabetes complicated by an episode of severe hypertriglyceridaemia-induced pancreatitis

Nathalie Denecker, Katelijn Decochez

Department of Endocrinology-Diabetes, UZ Brussel, Brussels, Belgium

Correspondence to

Dr Nathalie Denecker,
nathalie.denecker@uzbrussel.be

SUMMARY

A 23-year-old woman with a history of type 2 diabetes and non-compliance presented to the emergency department with abdominal epigastric pain and nausea. Laboratory examination revealed a mild ketoacidosis while an abdominal CT scan performed the following day demonstrated a severe acute pancreatitis of the body and tail (Balthazar grade E) despite normal amylase serum levels on admission. The presence of a lactescent serum was the clue to an extremely high triglyceride level ($>10\,000$ mg/dl) causing the pancreatitis. The hypertriglyceridaemia itself was attributed mainly to the diabetic ketoacidosis. There was no family history of hypertriglyceridaemia. The triad consisting of diabetic ketoacidosis, hypertriglyceridaemia and acute pancreatitis is an unusual presentation of poorly controlled diabetes which can occur in type 1 as well as type 2 diabetic adults and children. Treatment with intravenous insulin and hydration successfully resolved the ketoacidosis and hypertriglyceridaemia and reversed the episode of acute pancreatitis.

BACKGROUND

Although it is recognised that diabetic ketoacidosis may present with abdominal pain, it remains important to exclude an underlying acute pancreatitis which may be masked due to ambiguous presentation. Moreover, it has been demonstrated that in case of hyperlipidaemic serum normoamylasaemia can occur in more than half of the patients presenting with acute pancreatitis due to severe hypertriglyceridaemia.

With this unusual case we emphasise the need to perform an abdominal CT scan in case of persistent abdominal pain in ketoacidosis, especially in case of a hyperlipidaemic serum, even when inflammatory parameters are absent and clinical symptoms are only mild. Also this uncommon diagnosis should not be missed in children thus avoiding unnecessary surgical interventions for presumed acute abdominal conditions.

CASE PRESENTATION

A 23-year-old woman presented to the emergency department with abdominal epigastric pain which developed a few hours prior to admission together with nausea. The pain was continuously present without irradiation. There was no notion of fever and her defaecation pattern was normal.

The patient had been diagnosed with type 2 diabetes approximately 18 months earlier. At that time

she had been admitted in another hospital initially and had received insulin intravenously for 4 days, after which the treatment was switched to oral metformin 2×850 mg daily. From that moment on she only followed-up with her general practitioner and never returned to see the endocrinologist. She admitted of not always being compliant with her medication intake, certainly for the last few weeks.

She was diagnosed with a reflux oesophagitis in the past for which she was still taking pantoprazole 40 mg daily, and she had undergone a breast enlargement a few years before. She had stopped smoking since some time and only used alcohol during weekends, about twice a month, but in large amounts. She admitted regularly eating fatty food. Despite eating large amounts she had experienced about 10 kg of weight loss over the past few months. There was a history of diabetes in her paternal grandmother and in her maternal great-grandmother. Her father was diagnosed with prediabetes.

On admission she had a weight of 82 kg for a height of 168 cm and body mass index of 29 kg/m^2 . Physical examination revealed a blood pressure of 120/67 mm Hg, a pulse of 92/min and body temperature of 36.4°C . She was normally hydrated and had a Glasgow Coma Score of 15/15. The remainder of the physical examination was unremarkable except for epigastric tenderness without abdominal guarding and with normal bowel sounds.

INVESTIGATIONS

Initial laboratory parameters showed a glucose level of 460 mg/dl, blood urea nitrogen (BUN) 17 mg/dl, serum creatinine 0.57 mg/dl, sodium 132 mEq/l, potassium 3.9 mEq/l, chloride 98 mEq/l, bicarbonate 13 mEq/l (normal range 22–26 mEq/l), anion gap 25 mEq/l (normal range 10–18 mEq/l), lactate 1.1 mmol/l (normal range <2.2 mmol/l), calcium 9.2 mEq/l, total proteins 8.1 g/dl, lactate dehydrogenase 525 units/l, aspartate aminotransferase 18 units/l, alanine transaminase 22 units/l, amylase 98 units/l (normal range <113 units/l), lipase 946 units/l (normal range 50–200 units/l), C reactive protein 7.4 mg/l and white cell count $8300/\text{mm}^3$ with 65% neutrophils. The serum was extremely lactescent and turbid (figure 1) which prevented the dosage of haemoglobin and of coagulation parameters. Ketones were present in the urine (3+ measured by medi-test ketone test strip). Initial arterial blood gases at admission could not be interpreted due to insufficient sample, but a control sample 4 h later revealed a pH

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Figure 1 Appearance of hyperlipidaemic blood samples on admission.

7.40, $p\text{CO}_2$ 33 mm Hg, $p\text{O}_2$ 157 mm Hg, HCO_3^- 20 mEq/l, base excess -4 mEq/l.

Owing to remaining abdominal pain and increasing nausea with vomiting after correction of the ketoacidosis an abdominal CT scan was performed less than 24 h later. This showed a severe acute pancreatitis of the body and tail grade E according to the Balthazar CT severity index for acute pancreatitis (ie, presence of two or more fluid collections) (figure 2). There was no pancreatic necrosis observed.

Owing to important turbidity of the serum sample it was decided to measure triglycerides in the serum on the second day of admission which revealed triglycerides 12 851 mg/dl and a total cholesterol of 2004 mg/dl. Owing to the high triglycerides level low-density lipoprotein (LDL) cholesterol could not be calculated. For this reason the analyses for amylase and lipase were also repeated on the first sample, using a dilution of 1/40: amylase was then 188 units/l and lipase 1847 units/l (instead of 98 and 946 units/l, respectively), thus both clearly increased above the cut-off level. C-peptide was 0.26 ng/ml (normal range 0.85–3.25 ng/ml) with a glycaemia of 146 mg/dl and glycated haemoglobin (HbA1C) was 12.9%.

An ultrasound of the abdomen was performed when the patient had recovered to exclude a biliary cause for the pancreatitis, but this only confirmed discrete steatosis of the liver without gallstones.

DIFFERENTIAL DIAGNOSIS

Differential causes for a compensated metabolic acidosis such as prolonged fasting, lactate or alcoholic acidosis and renal insufficiency were excluded.

Initially the abdominal pain was attributed to the diabetic ketoacidosis, with acute pancreatitis and appendicitis in the differential diagnosis.

When the acute pancreatitis was diagnosed, the following causes had to be considered: biliary tract disease (gallstones), alcohol use, use of medication (eg, oral contraceptives), trauma, viral disease, autoimmune disease, hypercalcaemia or hyperlipidaemia.

Although this patient had been diagnosed with type 2 diabetes approximately 18 months before, we suspected a 'missed' type 1 diabetes due to the rather rapid and acute presentation of the illness with mild ketoacidosis, but this was excluded.

TREATMENT

On admission the patient was treated with fluid, insulin and potassium supplements intravenously. When the severe acute

Figure 2 A CT scan of the abdomen shows a swollen oedematous body and tail of the pancreas (arrow) with fluid collections surrounding the pancreas (triangle), one of which extends into the paracolic gutter (CT grade E acute pancreatitis).

pancreatitis was diagnosed the patient was transferred to the intensive care unit for monitoring and further treated conservatively with intravenous fluid, insulin and analgesics and was kept under fasting. After 4 days in the intensive care unit, the patient was transferred to the diabetes department again where the intravenous insulin was stopped and switched to subcutaneous insulin. The patient was discharged from the hospital on day 12 on an insulin regimen with three injections of insulin actrapid (~8 units) before each meal and insulin glargine (~24 units) before bedtime. Since triglycerides and cholesterol levels were still elevated a treatment with atorvastatin and fenofibrate was also initiated.

OUTCOME AND FOLLOW-UP

The evolution was favourable with normalisation of most laboratory parameters. There were neither any local complications of pancreatitis like pancreatic necrosis, an abscess or pseudocyst observed, nor were there signs of systemic

complications such as systemic inflammatory response syndrome present. Only triglycerides were still 549 mg/dl and total cholesterol 341 mg/dl at discharge. Autoimmune antibodies directed against insulin, glutamate decarboxylase (GAD65) and islet antigen-2 (IA-2) as well as islet cell antibodies (ICA) were all negative and C peptide had risen to 1.24 ng/ml (with a glycaemia of 159 mg/dl). There was no clear family history of hypertriglyceridaemia although a minor increase in LDL cholesterol was noted: laboratory data of her father revealed triglycerides 192 mg/dl, LDL cholesterol 157 mg/dl and HbA1C 6.2%, and her mother had triglycerides 62 mg/dl and LDL cholesterol 161 mg/dl.

Three months later her HbA1C had dropped to 6.5% but she had stopped taking fenofibrate and atorvastatin. Nine months after discharge she was admitted again in another hospital for poorly controlled diabetes (HbA1C 12.8%) with ketosis. Triglycerides at that time were 370 mg/dl, total cholesterol being 280 mg/dl and LDL-cholesterol 131 mg/dl with a normal CT scan of the pancreas. She was seen for the last time, 15 months after discharge from our hospital with a new improvement of her HbA1C to 8.2% and triglycerides, cholesterol and LDL-cholesterol levels, of 321, 243 and 135 mg/dl, respectively. There have been no additional episodes of pancreatitis up until 15 months follow-up.

DISCUSSION

We reported on a 23-year-old patient with type 2 diabetes presenting with abdominal pain and a mild diabetic ketoacidosis associated with an acute pancreatitis and very important hypertriglyceridaemia.

Diabetic ketoacidosis is well known to occur in type 1 diabetes and is due to an absolute insulin deficiency, but can also occur in type 2 diabetes in association with an excess of counter-regulatory hormones.^{1 2} This clinical condition which is like an intermediate between type 1 and type 2 diabetes has been termed ketosis-prone type 2 diabetes³ which was confirmed in this patient.

Hyperamylasaemia as well as hyperlipasaemia are both well known to occur frequently in diabetic ketoacidosis without an underlying acute pancreatitis. Yadav *et al* reported non-specific elevations of amylase and lipase in, respectively, 16.6% and 24.6% of diabetic ketoacidosis episodes. In this patient the initial lipase level was elevated to more than three times the upper limit of the normal with a normal amylase level at admission. Although the elevation of either amylase or lipase to >3 times the normal is highly suggestive for acute pancreatitis, it is not sufficient for the diagnosis of it.⁴ Owing to mild clinical and biological signs, a CT scan was not performed directly since it could have been falsely negative. Moreover, both the amylase and lipase values were underestimated in this patient due to interference with the coexisting hypertriglyceridaemia. Serum amylase can indeed be falsely low or normal in up to 50% of patients with hypertriglyceridaemia-induced pancreatitis. This is attributed to either the interference of the plasma lipids with the colorimetric amylase assay or the presence of an inhibitor in the plasma which inhibits the assay,⁵ and an increase in the non-aqueous phase of the sample due to hyperlipidaemia.^{6 7} If the lipaemic serum is diluted, the amylasaemia will increase and usually the lipase levels as well, which was the case in this patient.

Hypertriglyceridaemia is a known but rare cause of acute pancreatitis. Fortson *et al*⁸ reported this as the aetiological factor for pancreatitis in 1.3–3.5%. This entity should be distinguished from the mild hyperlipidaemia which results from an acute pancreatitis, particularly alcoholic pancreatitis, which is much more frequent.⁹ The mechanism by which hypertriglyceridaemia can

lead to pancreatitis is most likely because of high triglycerides or chylomicrons in the pancreatic capillaries being hydrolysed by pancreatic lipase, which leads to free fatty acid release, causing trypsinogen release and injury of the acinar cells and capillaries. In general, a triglycerides level of >1000 mg/dl is necessary for causing an acute pancreatitis, which is also the level at which serum becomes lactescent.¹⁰ Lipaemic or lactescent serum is often the clue to diagnosis of the pancreatitis although this finding can be regularly overlooked.^{8 9 11}

In this case we noted a very severe hypertriglyceridaemia which can either be of genetic or acquired origin resulting from metabolic disorders (eg, diabetes), diet (including alcohol and obesity) and/or drugs.⁹ Acute pancreatitis secondary to hypertriglyceridaemia is most commonly encountered in a poorly controlled diabetic.⁸ Yadav *et al*⁹ argue that none of these secondary factors independently would increase the triglycerides levels to such an extent to cause an acute pancreatitis, but that this will happen in case of a pre-existing defect in lipoprotein metabolism. However, it was demonstrated that most patients with diabetic ketoacidosis and severe hypertriglyceridaemia (>1000 mg/dl) did not have an underlying genetic hyperlipidaemia which contributed to their original severe hypertriglyceridaemia.¹² In our patient familial hypertriglyceridaemia was unlikely since triglycerides levels were nearly normal in both parents. We believe that the hypertriglyceridaemia was most likely due to the uncontrolled diabetes with mild compensated ketoacidosis, in combination with the fact that our patient kept eating fatty food until then, that she sometimes had bouts of excessive drinking and that she was taking pantoprazole which can be a very rare cause of hypertriglyceridaemia. Fulop and Eder¹² indeed noticed that the patients with diabetic ketoacidosis with most severe hypertriglyceridaemia only had mild acidemia and were often less-severely ill, allowing them to eat until hospitalisation. There have been a few other reports in children on the clinical triad of severe hypertriglyceridaemia in diabetic ketoacidosis associated with acute pancreatitis where no other underlying risk factor for the hypertriglyceridaemia, apart from the newly diagnosed diabetic ketoacidosis, could be detected.^{6 11} The mechanism by which diabetic ketoacidosis leads to hypertriglyceridaemia is well recognised. Insulin deficiency activates lipolysis in adipose tissue which facilitates the availability of free fatty acids as substrates for triglycerides synthesis in the liver, thus inducing a high flux of very low-density lipoprotein into the circulation. At the same time reduced activity of lipoprotein lipase due to shortage of insulin causes inadequate removal of triglycerides from the plasma, leading to hypertriglyceridaemia. The administration of insulin will have an important hypolipidaemic effect mainly due to clearance of triglycerides from plasma and is thus the cornerstone of treatment in a patient with diabetic hyperlipidaemia.¹³ It was also beneficial for the remission of the acute pancreatitis in our patient.

In conclusion, based on the above discussion it is most likely that the uncontrolled diabetes with ketoacidosis was the initiating event for the hypertriglyceridaemia in our patient leading to subsequent acute pancreatitis. This sequence of events has also been suggested in other case reports which reported on the coexisting clinical triangle of diabetic ketoacidosis, hypertriglyceridaemia and acute pancreatitis.^{6 13 14 15} Hyperlipidaemia as a primary cause for the acute pancreatitis complicated by diabetic ketoacidosis remains another possibility in this patient. Her triglycerides returned however to a baseline level of around 300 mg/dl without fenofibrate intake, which is unlikely to induce acute pancreatitis. In any case an acute pancreatitis

should be considered in a patient with abdominal pain and diabetic ketoacidosis, in particular in the presence of lipaemic serum, even in the absence of inflammatory signs and the presence of mild clinical symptoms.

Learning points

- ▶ The clinical triad consisting of diabetic ketoacidosis, hypertriglyceridaemia and acute pancreatitis is an unusual presentation of poorly controlled diabetes, which can occur in type 1 as well as type 2 diabetic adults and children.
- ▶ In diabetic ketoacidosis amylase and lipase levels can be elevated without the presence of an underlying acute pancreatitis.
- ▶ In case of severe hypertriglyceridaemia amylase and lipase levels can be falsely low or normal even in the presence of acute pancreatitis and must be rechecked after dilution of the serum.
- ▶ In a patient with diabetic ketoacidosis and persistent abdominal pain despite an appropriate treatment of the ketoacidosis a CT scan is necessary to exclude or confirm an acute pancreatitis which may be masked due to ambiguous presentation, especially when severe hypertriglyceridaemia or a lactescent serum is present. This applies in particular to patients without any inflammatory parameters, normal amylase and lipase levels and only mild clinical symptoms.
- ▶ Institution of insulin intravenously is the cornerstone of treatment which resolves ketoacidosis and hypertriglyceridaemia and reverses acute pancreatitis.

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