CASE REPORT

Ominous triad triggered by high-dose glucocorticosteroid therapy

Sarah Bär,¹ Fritz Daudel,² Thomas Zueger¹¹Division of Internal Medicine, Hospital Tiefenau, Inselgruppe AG, University of Bern, Bern, Switzerland²Division of Intensive Care, Hospital Tiefenau, Inselgruppe AG, University of Bern, Bern, Switzerland**Correspondence to**Dr Thomas Zueger,
thomas.zueger@spitaltiefenau.ch

Accepted 26 April 2017

SUMMARY

Glucocorticosteroids (CS) play a key role in the treatment of numerous diseases. Nonetheless, they can be accompanied by several adverse effects. We present the case of a 51-year-old woman who was treated with high-dose CS for a relapse of her multiple sclerosis. After 5 days of treatment, the patient developed severe diabetic ketoacidosis, hypertriglyceridemia and acute pancreatitis—a potentially life-threatening triad which has previously been described, in our case, however, for the first time as a complication of CS therapy. Our patient's condition was further aggravated by a circulatory shock, haemodynamic relevant bleeding from a duodenal ulcer and psychotic symptoms. In the intensive care unit, intravenous insulin infusion, fluid resuscitation, catecholamine support, electrolyte supplementation, endoscopic haemoclipping and antibiotic and antipsychotic treatment were administered, leading to a continuous improvement of the patient's health state.

BACKGROUND

Owing to their anti-inflammatory and immunosuppressive effects, glucocorticosteroids (CS) are widely used in medical treatment. Besides their well-known beneficial role, CS have numerous adverse effects.¹ High-dose CS commonly lead to deterioration of glucose metabolism¹ but are rarely the source of diabetic ketoacidosis (DKA).^{2–4} A further rare but severe CS-related side effect is acute pancreatitis.^{5–11} The underlying pathophysiologic mechanisms are not yet fully elucidated.¹⁰ However, CS are known to promote hypertriglyceridemia (HTG),¹ which is a well-established cause of pancreatitis.^{12–13} The coexistence of DKA, HTG and pancreatitis has been described in other case reports and they seem to be linked in a multidirectional cause–effect relationship.^{14–20} Although the individual components of the described triad have been reported previously in the context of CS medication, there is no documented case with this ominous triad of DKA, HTG and pancreatitis induced by CS therapy.

CASE PRESENTATION

A 51-year-old woman was brought to our emergency ward presenting with progressive confusion, slurred speech, dyspnoea and extensive thirst for the last 3 days. On admission, the patient was tachypnoeic (30/min), tachycardic (166/min), normotensive and afebrile; oxygen saturation was 100%, and

Glasgow Coma Scale was 12 (E3/V3/M6). The clinical examination revealed moderate tenderness on epigastric palpation accompanied by reduced bowel sounds and a diminished sensation of feet, fingers, neck and tongue.

The patient was diagnosed with multiple sclerosis (MS) 16 years ago. Due to a fifth relapse of her relapsing-remitting MS with the aforementioned paraesthesia and hypoesthesia accompanied by intense subjective discomfort and huge psychological strain, her neurologist started to treat her with oral methylprednisolone, 500 mg daily, for the past 5 days prior to admission. Apart from an arterial hypertension treated with candesartan, hydrochlorothiazide and metoprolol, no additional health issues were known by the time of primary survey.

INVESTIGATIONS

As summarised in tables 1–3, laboratory studies revealed a hyperglycaemic state (plasma-glucose 46 mmol/L) in combination with acidosis (pH 7.1) and ketonuria. We observed an acute kidney injury with oligoanuria and severe dyselektrolytemia without sonographic evidence of postrenal pathologies. We postulated a severe DKA of a previously unknown diabetes mellitus triggered by high-dose CS therapy. The patient was transferred to the intensive care unit (ICU) for further treatment. During the first hours in the ICU, the patient developed extensive epigastric pain with abdominal defence and haemodynamic instability. Additional laboratory investigations showed marked elevations of amylase, lipase and CRP. Serum lipids were severely elevated with triglycerides of 26.7 mmol/L (table 3). CT scan of the abdomen confirmed an exudative pancreatitis (figure 1) with bilateral pleural effusions (figure 2).

DIFFERENTIAL DIAGNOSIS

Although a fasting glucose value obtained 2 years ago was in the normal range, based on the HbA1c value of 11.1% on admission, a pre-existing disorder of glucose metabolism must be assumed. With a BMI of 29.5 kg/m², the patient was overweight and therefore at increased risk to suffer from insulin resistance and hence develop type-2 diabetes mellitus (DM2). The current finding of DKA in our patient and the undetectably low serum insulin levels on admission (<1 mU/L) suggest a severe beta-cell dysfunction. Both insulinoma-associated-2 and glutamin-decarboxylase antibodies were negative, speaking against a type-1 diabetes

CrossMark

To cite: Bär S, Daudel F, Zueger T. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220328

Table 1 Arterial blood gas analysis on admission

pH (7.370–7.450)	7.10
pCO ₂ (32–43 mm Hg)	10.1
pO ₂ (71–104 mm Hg)	171.9
HCO ₃ (21–26 mmol/L)	3.1
Base excess (−2.0 to 3.0)	−24.1
Lactate (0.5–1.6 mmol/L)	2.7

Pathological values are printed in bold.

mellitus. Given these findings, we interpreted the DKA in the context of the acute pancreatitis and CS therapy based on a pre-existing DM2.

CT scan of the abdomen and laboratory workup revealed no signs for an obstructive, neoplastic or infectious source of the pancreatitis. Calcium level was normal. Alcohol and nutritional anamnesis was unremarkable and the family anamnesis negative for hereditary pancreatitis. Of note, fasting triglyceride levels obtained 1 year ago were slightly elevated (2.71 mmol/L), raising the suspicion of a pre-existing lipid disorder. Given the markedly increased triglycerides on admission, we postulated a hyperlipidemic pancreatitis induced by the CS-mediated metabolic disorders.

TREATMENT

In the ICU, intravenous insulin infusion, fluid resuscitation and electrolyte correction were initiated. Blood glucose levels were lowered by administration of 5–6 units of intravenous insulin (aspart) per hour aiming at a blood-glucose level of 10 mmol/L within 48 hours.

OUTCOME AND FOLLOW-UP

In the initial course, the patient developed a circulatory shock which was treated with fluid resuscitation and catecholamine support. Despite missing ct-graphic signs of necrotizing pancreatitis, a therapy with tazobactam/piperacillin for 5 days was added due to a Ranson's criteria for pancreatitis mortality of 5 points after 48 hours (initially 3 points), newly developed urinary tract infection and septic condition. The patient was initially kept in a fasting state and later a gastrojejun tube was placed for nutrition. In the course of her illness, the patient developed psychotic symptoms which responded well to therapy with oral haloperidol. Furthermore, the patient showed duodenal ulcer bleeding (Forrest IIa), which was treated with five erythrocyte concentrates, 3 g tranexamic acid and two endoclips. Of note, the psychotic symptoms and duodenal bleeding could also have been attributable to the high-dose CS therapy.

On day 5, intravenous insulin therapy was switched to a subcutaneous intensified conventional insulin therapy (ICT) with insulin glargine and aspart. The CS were gradually reduced every 2–3 days. The renal function slowly returned to normal. Epigastric pain and CRP elevation, however, persisted. Besides a progression of right-sided pleural effusion, a second CT scan showed no secondary complications of the acute pancreatitis. A

Table 2 Urine analysis on admission

Leucocytes (negative)	negative
Nitrite (negative)	negative
pH (5.0–6.0)	5.5
Protein (negative)	1+
Glucose (negative)	4+
Ketone bodies (negative)	3+
Bacteria (<125/μL)	negative

Pathological values are printed in bold.

Table 3 Laboratory values on admission and day 1

	On admission	Day 1
Glucose (4.1–6.05 mmol/L)	46.5	16
Sodium (132–146 mmol/L)	135	141
Potassium (3.4–4.5 mmol/L)	5.1	4.5
Calcium corrected (2.15–2.50 mmol/L)	2.25	
Calcium ionised (1.16–1.32 mmol/L)		0.99
Chloride (98–107 mmol/L)	82	
Magnesium (0.66–1.07 mmol/L)	1.71	1.11
Phosphate (0.81–1.45 mmol/L)	3.43	0.18
Osmolarity (280–300 mOsm/kg)	386	
Urea (<8.3 mmol/L)	21.9	
Creatinine (44–80 μmol/L)	176	157
Bilirubin total (<21 μmol/L)	15.5	10.2
ASAT (<35 U/L)	90	64
ALAT (<35 U/L)	65	40
g-GT (<40 U/L)	110	490
Alkaline phosphatase (35–100 U/L)	90	34
Amylase (13–53 U/L)		313
Lipase (13–60 U/L)		1995
CRP (<5 mg/L)	4	177
HbA1c (4.8%–5.9%)	11.1	
Cholesterol (<5.2 mmol/L)		12.9
Triglycerides (<2.30 mmol/L)		26.7
Haemoglobin (121–154 g/L)	166	152
Thrombocytes (140–380 G/L)	282	108
Leucocytes (3.5–10.5 G/L)	17.0	10.9
Band neutrophil cells (3.0%–18.0%)	22.5	58.5
Segmented neutrophil cells (40%–66%)	58	29

Day 1 denotes laboratory values on the first day after admission. ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; g-GT, gamma glutamyltransferase; HbA1c, glycated hemoglobin.

Pathological values are printed in bold.

chest tube was inserted to drain the pleural effusion (amylase-rich pancreatic fluid). The drainage was removed after 4 days. On day 11, the patient was transferred to the normal ward. A oral diet was gradually established and the gastrojejun tube was removed. Until hospital discharge, steroids were reduced

Figure 1 CT scan axial view showing exudative pancreatitis (marked by arrows).

Figure 2 CT scan axial view showing bilateral pleural effusions (marked by arrows).

to 2.5 mg prednisolone daily, and blood glucose was near-normal under on-going adaptation of the ICT. The patient was discharged on day 25 in good health state.

DISCUSSION

HTG,²¹ DKA^{2–4} and acute pancreatitis are all separately reported side effects of CS therapy.¹⁰ Furthermore, the combination of HTG, DKA and acute pancreatitis is described in a couple of patients,^{14–20} but this is the first documented case, in which this triad was induced by CS. Cause and effect of this ominous triad are discussed controversially but they seem to be linked in a multidirectional relationship. A recent Swedish nationwide case–control study showed increased risk for acute pancreatitis in patients under oral CS.¹¹ The mechanisms by which CS induce pancreatitis are not yet fully elucidated.¹⁰ However, it was postulated that a CS-induced HTG with lipid-dependent obstruction of pancreatic capillaries resulting in local ischemia and inflammation may be the cause.^{6,10} The threshold-level of triglycerides to cause pancreatitis was estimated to be around 10 mmol/L.¹³ However, new data suggest that even lower levels of triglycerides (2 mmol/L) enhance the risk for pancreatitis.²² Hypertriglyceridemic pancreatitis usually occurs in patients with pre-existing lipid disorders in combination with a second risk factor such as uncontrolled diabetes mellitus. This is in line with our findings

of markedly elevated triglycerides on admission and a pre-existing slight HTG. High-dose CS and consecutive deteriorated glucose-metabolism induced a secondary HTG. It is conceivable that the hyperlipidaemia and resulting pancreatitis with concomitant insulin deficiency promoted the DKA resulting in further aggravation of this vicious circle.

Taken together, in the present case, a usually harmless therapeutic intervention resulted in a life-threatening complication and should remind one to carefully evaluate the patient's metabolic state before initiating a high-dose CS therapy.

Acknowledgements The authors thank Dr med D Sieron and the Radiology Department for providing the radiological images, Dr med Frédéric Walser for providing laboratory results and Prof Dr HP Kohler for his support.

Contributors SB, FD and TZ were all involved in the treatment of the patient. SB and TZ drafted the manuscript and FD thoroughly revised the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- Schäcke H, Döcke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol Ther* 2002;96:23–43.
- Cağdaş DN, Paç FA, Cakal E. Glucocorticoid-induced diabetic ketoacidosis in acute rheumatic fever. *J Cardiovasc Pharmacol Ther* 2008;13:298–300.
- Agarwal DK, Jeloka T, Sharma AP, et al. Steroid induced diabetes mellitus presenting as diabetic ketoacidosis. *Indian Journal of Nephrology* 2002;12:122–3.
- Jaja TAI, Eke FU, Anochie IC. Steroid induced Diabetic Ketoacidosis (DKA) in a 13 year old female with renal disorder. *Pediatrics & Therapeutics* 2012;2:109.
- Barr HS, Wolff OH. Pancreatic necrosis in cortisone-treated children. *Lancet* 1957;272:812–5.
- Bhavsar B, Bhatt A. Steroid induced hyperlipidemic pancreatitis and new onset diabetes mellitus. treatment with plasmapheresis. *JOP* 2008;9:664–5.
- Bourne MS, Dawson H. Acute pancreatitis complicating prednisolone therapy. *Lancet* 1958;2:1209–10.
- Levine RA, McGuire RF. Corticosteroid-induced pancreatitis: a case report demonstrating recurrence with rechallenge. *Am J Gastroenterol* 1988;83:1161–4.
- Marczynska-Robowska M. Pancreatic necrosis in a case of still's disease. *Lancet* 1957;272:815–6.
- Nelp WB. Acute pancreatitis associated with steroid therapy. *Arch Intern Med* 1961;108:702–10.
- Sadr-Azodi O, Mattsson F, Bexelius TS, et al. Association of oral glucocorticoid use with an increased risk of acute pancreatitis: a population-based nested case-control study. *JAMA Intern Med* 2013;173:444–9.
- Scherer J, Singh VP, Pitchumoni CS, et al. Issues in hypertriglyceridemic pancreatitis: an update. *J Clin Gastroenterol* 2014;48:195–203.
- Yadav D, Pitchumoni CS. Issues in hyperlipidemic pancreatitis. *J Clin Gastroenterol* 2003;36:54–62.
- Hahn SJ, Park JH, Lee JH, et al. Severe hypertriglyceridemia in diabetic ketoacidosis accompanied by acute pancreatitis: case report. *J Korean Med Sci* 2010;25:1375–8.
- Lutfi R, Huang J, Wong HR. Plasmapheresis to treat hypertriglyceridemia in a child with diabetic ketoacidosis and pancreatitis. *Pediatrics* 2012;129:e195–e198.
- Nair S, Pitchumoni CS. Diabetic ketoacidosis, hyperlipidemia, and acute pancreatitis: the enigmatic triangle. *Am J Gastroenterol* 1997;92:1560–1.
- Rius Riu F, Pizarro Lozano E, Reverter Calatayud JL, et al. [Acute pancreatitis in newly diagnosed type I diabetes mellitus with diabetic ketoacidosis and hypertriglyceridemia]. *Med Clin* 1993;101:622–4.
- Singla AA, Ting F, Singla A. Acute pancreatitis secondary to diabetic ketoacidosis induced hypertriglyceridemia in a young adult with undiagnosed type 2 diabetes. *JOP* 2015;16:201–4.
- Winter RJ, Herr TJ, Stone NJ, et al. Diabetic lipemia in childhood diabetic ketoacidosis: a clue to coexisting acute pancreatitis. *Diabetes Care* 1980;3:706–7.
- Wolfgang PM, Macdonald MJ. Severe Hypertriglyceridemia Causing acute pancreatitis in a child with New Onset type I Diabetes Mellitus presenting in Ketoacidosis. *J Pediatr Intensive Care* 2013;2:77–80.
- Arnaldi G, Scandali VM, Trementino L, et al. Pathophysiology of dyslipidemia in Cushing's syndrome. *Neuroendocrinology* 2010;92(Suppl 1):86–90.
- Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting Mild-to-Moderate hypertriglyceridemia and risk of acute pancreatitis. *JAMA Intern Med* 2016;176:1834–42.

Learning points

- Besides their well-known adverse effects, glucocorticosteroids (CS) may induce rare but potentially life-threatening complications.
- Diabetic ketoacidosis, hypertriglyceridemia and acute pancreatitis can occur as a triad and be induced by CS therapy.
- Abdominal pain occurring in CS therapy should raise the suspicion not only for gastric/duodenal ulcer but also for pancreatitis.
- Before starting and in the course of high-dose CS therapy, metabolic assessment including lipid-panel and glucose homeostasis should be performed.
- With regard to the possibly serious adverse events, aggressive therapy for a mild relapse of multiple sclerosis should be carefully considered.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow