

Streptozotocin-induced diabetic ketoacidosis in a patient with metastatic islet-cell carcinoma

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ABSTRACT

Here we report a severe life-threatening complication of treatment with streptozotocin in a patient with pancreatic island-cell carcinoma. The patient was admitted to the intensive care unit with severe diabetic ketoacidosis which needed aggressive fluid resuscitation and insulin therapy. We believe it is critical to be aware of the symptoms of diabetic ketoacidosis and monitor glucose levels during streptozotocin treatment.

KEY WORDS

Clinical oncology, streptozotocin, carcinoma neuroendocrine, diabetic ketoacidosis

INTRODUCTION

Streptozotocin is an antibiotic isolated from *Streptomyces acromogenes*. In oncology streptozotocin is used as a cytotoxic agent to treat islet-cell carcinoma. In functionally active carcinomas streptozotocin is effective in reducing the symptoms of insulin-induced hypoglycaemia.¹ Furthermore, combination with 5-fluorouracil leads to a superior duration of survival compared with streptozotocin monotherapy.² Combinations of 5-FU and streptozotocin or doxorubicin and streptozotocin have long been the gold standard chemotherapy regimen for unresectable pancreatic islet-cell tumours.³ Only recently, promising results for new targeted treatments such as the tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus were reported.^{4,5} We describe the case of a 48-year-old woman treated with streptozotocin, who developed a *de novo* diabetic ketoacidosis. To our knowledge this is the first reported case of streptozotocin-induced ketoacidosis in humans.

CASE REPORT

A 48-year-old woman presented to the department of medical oncology with tachypnoea and general weakness. Three years before, she had been diagnosed with metastatic non-secreting low-grade neuroendocrine pancreatic islet-cell carcinoma. She had been treated with streptozotocin and 5-fluorouracil intravenously every six weeks since diagnosis. Computer tomography (CT) scanning one month prior to presentation to the emergency department showed stable disease after 27 cycles of chemotherapy. The last cycle was completed six days before presentation. Physical examination revealed a respiratory rate of 40 breaths/minute, but was otherwise unremarkable. Blood biochemistry showed (normal values between brackets): arterial pH 6.90 (7.36-7.44), pO₂ 19.7 kPa (10.0-13.3), pCO₂ 0.9 kPa (4.7-6.4), bicarbonate 1.4 mmol/l (22-29) and base excess -29.9 mmol/l (-3-3). The blood glucose level was highly elevated: 28 mmol/l (4.0-5.6). Urinalysis was positive for ketones. Serum antiglutamate decarboxylase (GAD) antibodies were not detectable. We diagnosed *de novo* severe diabetic ketoacidosis. She received intensive fluid resuscitation, intravenous bicarbonate and insulin. Long-acting insulin was started and streptozotocin therapy was discontinued. One year after presentation the patient is still dependent on insulin therapy.

DISCUSSION

The diabetogenic action of streptozotocin was first discovered in 1963.⁶ Since then it has been widely used to induce a hyperglycaemic state in animal models studying the pathogenesis of diabetes. It produces a permanent diabetic state in animal models through direct destruction of the pancreatic beta cells. Diabetes

becomes evident after 24 hours of treatment and pancreatic insulin levels fall to 5% of their initial value.⁷ It is noteworthy, however, that our patient only developed severe hyperglycaemia after 27 cycles (67.5 g/m²) of streptozotocin. Indeed, a cumulative toxic effect has been observed in animal models.⁸ In an earlier clinical study, however, patients with islet cell tumours received up to 80 g/m² of streptozotocin without developing diabetic ketoacidosis.⁹ Since the recent CT scan of this patient showed stable disease without gross involvement of the pancreas, we believe that the hyperglycaemic state could not be explained by pancreatic failure due to tumour progression. Therefore, we conclude that the severe diabetic ketoacidosis in this patient was caused by streptozotocin. To the best of our knowledge this is the first reported case of streptozotocin-induced diabetic ketoacidosis in humans. We advise oncologists to monitor glucose levels during streptozotocin treatment.

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