Capecitabine-induced hyperosmolar hyperglycaemic state

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SUMMARY

An elderly woman with metastatic breast cancer was admitted with hyperglycaemic hyperosmolar state (HHS) and an elevated haemoglobin A1C. For 1 week, she had experienced confusion, nausea and frequent urination. Preceding this, she had completed seven cycles of capecitabine chemotherapy for her breast cancer. She did not have a history of diabetes prior to chemotherapy. Given the temporal dysglycaemia following the patient's chemotherapy regimen, capecitabine was thought to be a probable offending agent. The patient was acutely treated for HHS, and was discharged on a basal-bolus insulin regimen. Her capecitabine was held pending review with her oncology team. The patient was ultimately titrated down to basal insulin only by her family doctor. Given the common use of capecitabine, it is important to recognise the risk of hyperglycaemic and hyperglycaemic emergencies as potential adverse effects. This highlights the need to monitor blood glucose throughout treatment to prevent hyperglycaemic emergencies.

BACKGROUND

Capecitabine is an orally administered prodrug of 5-fluorouracil (5-FU), which is often used for treatment of solid tumour cancers such as breast cancer and gastrointestinal tumours. Common adverse effects include nausea, diarrhoea, anorexia and erythrodysthesia (hand-foot syndrome). However, there have been case reports of metabolic disturbances linked to capecitabine including hyperlipidaemia, and less commonly, hyperglycaemic. We report a case of a new diagnosis of persistent diabetes mellitus following an acute presentation of hyperosmolar hyperglycaemic syndrome (HHS) subsequent to treatment with the chemotherapy agent, capecitabine. With increasing indications for the use of capecitabine in treating malignancy, clinicians should be aware of the drug's rare adverse events and potentially consider regular monitoring of blood glucose throughout treatment to avoid hyperglycaemic emergencies.

CASE PRESENTATION

A 72-year-old, non-obese woman presented to her family doctor with a 7-day history of malaise, nausea, decreased appetite, polydipsia, increased urinary frequency and nocturia without dysuria. She had no history of fevers, chills, rigours, flank pain or any other infectious symptoms. Bloodwork ordered by the family doctor revealed a random blood glucose of 40.2 mmol/L (normal range 4.0–11.0 mmol/L) and the patient was subsequently advised to present to hospital. On initial presentation to the hospital, the patient's heart rate was 124 beats per minute with a blood pressure of 142/69 mm Hg. She examined hypovolaemic and as such, was given a 2 L bolus of intravenous fluid, which subsequently lowered her heart rate to 104 beats per minute. Her Glasgow Coma Scale was scored at 14, with one point subtracted for verbal response. The patient's investigations revealed a random blood glucose of 39.4 mmol/L, serum osmolality of 362 mmol/kg (normal range 285–295 mmol/kg), detectable ketones and a normal pH of 7.33. Her haemoglobin A1C (HbA1C) was elevated at 8.8%. She was initiated on treatment for HHS. She received one dose of empiric antibiotics due to an initial positive urinalysis and gram positive cocci (not speciated); however, repeat urine culture did not indicate any significant growth.

The patient's history was significant for metastatic breast cancer for which she had received seven cycles of capecitabine over the span of 7 months up until presentation. Prior to starting capecitabine treatment, she had no history of diabetes mellitus, and her haemoglobin A1C was 6.3%. She was not on any other medications that may have induced hyperglycaemic or HHS.

INVESTIGATIONS

Prior the capecitabine initiation, the patient had an HbA1C of 6.3%, consistent with pre-diabetes, and a normal triglyceride level of 0.73 mmol/L (normal <1.7 mmol/L). Following seven cycles of capecitabine over a span of 7 months, there was an increase in her HbA1C to 8.8% and a random plasma glucose 39.4 mmol/L. The patient's triglyceride level had also risen to 1.56 mmol/L. CT scans from her oncology team to assess disease progression did not show any focal lesions in the pancreas prior to or at the time of her admission that may have caused pancreatic beta-cell insufficiency.

A summary of investigations prior to capecitabine initiation and on admission are outlined in table 1.

DIFFERENTIAL DIAGNOSIS

Although the patient did receive one dose of empiric intravenous antibiotics for treatment of a possible urinary tract infection, the patient's symptoms of polyuria, malaise and dehydration can be better explained by her hyperglycaemic state. Notably, this patient had absence of dysuria, fever and repeat urine culture was bland, making a urinary tract infection less likely to be the sole cause of her presentation. Furthermore, improved glycaemic control without any further antibiotic doses resolved the patient's symptoms which again points away from a true underlying urinary tract infection precipitating her HHS. A review of the patient's medications did not reveal any drugs such as corticosteroids or atypical antipsychotics that may have caused the hyperglycaemic. Given the patient's known metastatic breast cancer, there was also a consideration

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Table 1 Summary of patient investigations prior to capecitabine initiation and on admission

Prior to capecitabine initiation	On admission
A1C: 6.3%	A1C: 8.8%
Lipid Panel:	Lipid Panel:
Cholesterol 4.15 mmol/L	Cholesterol 2.35 mmol/L
Triglyceride 0.73 mmol/L	Triglyceride 1.56 mmol/L
HDL 2.10 mmol/L	HDL 9.85 mmol/L
LDL 1.72 mmol/L	(LDL not able to be calculated)
Non HDL 2.05 mmol/L	Non HDL 1.50 mmol/L
	Random plasma glucose 39.4 mmol/L
	Serum osmolality 362 mmol/kg
	Beta hydroxybutyrate 1.6 mmol/L
	Venous blood gas: pH 7.33, Bicarbonate 29 mmol/L, lactate 2.6 mmol/L
	Kidney Function
	Sodium 151 mmol/L
	Potassium 4.9 mmol/L
	Creatinine 114 umol/L
	Liver Enzymes
	ALT 14 U/L
	AST 14 U/L
	ALP 159 U/L
	GGT 34 U/L
	Total bilirubin 9 µmol/L

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL, high density lipoprotein; LDL, low density lipoprotein.

for a potential metastatic pancreatic lesion resulting in pancreatic insufficiency. Notably, however, a current CT scan prior the patient's admission did not reveal any pancreatic lesions. A repeat CT scan done during the patient's hospitalisation in fact revealed a reduction in her known metastatic lesions and no new lesions in the pancreas. While considered to be in the prediabetic range prior to capecitabine initiation, the patient's HbA1C had risen dramatically within 7 months of capecitabine therapy, from 6.3% to 8.8%. Given the temporal relation with capecitabine therapy and its known, although rare, association with hyperglycaemic, capecitabine was thought to be the inciting factor for the patient's HHS presentation.

TREATMENT

The patient was treated with intravenous fluids and an insulin infusion. Given that the patient presented in a decompensated metabolic state, the patient was transitioned to a subcutaneous insulin regimen prior to discharge. The patient's initial blood sugars were difficult to control with only a basal insulin regimen, and ultimately, required the addition of mealtime rapid acting insulin boluses. She was finally stabilised with a basal-bolus insulin regimen of glargine 15 units in the morning and lispro 8 units with meals prior to discharge. As this was a new diagnosis of diabetes mellitus, she was connected with the diabetes nurse educator in hospital prior to discharge. Capecitabine was suspended at discharge pending outpatient review with the patient's oncology team. She was discharged with close follow-up by her family doctor.

OUTCOME AND FOLLOW-UP

Following discharge, the patient was followed closely by her family doctor as well as the community multidisciplinary diabetes team. Her oncology team also elected to hold her subsequent cycles of capecitabine. Ultimately, the patient was able to discontinue short acting insulin and titrate her glargine insulin down to 10 units daily while maintaining her glucose within the optimal range.

DISCUSSION

Capecitabine is an orally administered prodrug of 5-FU, a pyrimidine analogue that acts as an antimetabolite to inhibit cell growth through its interference with DNA and RNA synthesis.[1] It is indicated for the treatment of metastatic breast cancer and gastrointestinal cancers. Due to its selective tissue metabolism, capecitabine is generally better tolerated than its earlier generation chemotherapeutic relative, 5-FU. The most common adverse reactions to capecitabine include nausea, anorexia, diarrhoea and palmar-plantar erythrodysesthesia (hand-foot syndrome).[2] There have, however, been rare cases reported of capecitabine induced hypertriglyceridaemia and hyperglycaemic in the diabetic range[2 3] and only one reported case of hyperglycaemic alone.[4] None of these documented cases have been associated with HHS.

Although the mechanism behind capecitabine-induced hyperglycaemic remains unclear, hyperglycaemic is a well-known side effect of many chemotherapeutic agents.[5] Hyperglycaemic induced by drugs can be a result of a variety of mechanisms, including altered insulin secretion and sensitivity, direct cytotoxic effects on pancreatic insulin producing beta-cells, promotion of glycogenolysis or hepatic gluconeogenesis.[5] Capecitabine is metabolised into 5-FU sequentially by three enzymes: carboxylesterase (predominantly located in liver and hepatomas), cytidine deaminase (located in the liver and various solid tumour tissues) and thymidine phosphorylase (located in various solid tumour and normal tissues).[6] Given the high levels of enzyme activity in the liver, fluorouracil has been linked to mild and transient serum aminotransferase elevations.[1] This liver dysfunction has been postulated to interfere with triglyceride metabolism in the liver and may also alter glucose metabolism.

Tegafur-uracil is another 5-FU prodrug, for which there have been two case reports of not only associated hyperglycaemic but also fulminant type 1 diabetes.[7 8] Similar to capecitabine, tegafur is hepatically metabolised via thymidine phosphorylase to 5-FU.[9] It was postulated that 5-FU caused the diabetes through direct cytotoxic effects on the pancreatic beta-cells. 5-FU can stimulate chemokine ligand 10 and interleukin 18 in pancreatic islet beta cells; these immune mediators in turn activate T cells and macrophages leading to beta cell destruction via cell mediated T cell infiltration.[7 9] A clue to the aetiology of hyperglycaemic in our case with capecitabine are the presence of several case reports of pancreatitis linked to its use, suggesting direct beta-cell damage is possible.[10 11] Conversly, it remains possible that the inciting trigger for pancreatitis may be indirect, and instead due to capecitabine-induced hypertriglyceridaemia.[12] Evidence against this being the sole cause for the pancreatitis includes the report of several cases of pancreatitis in the setting of capecitabine therapy when triglyceride levels remained normal.[10 11] It has been suggested that the 5-FU-based chemotherapeutic class may induce both an acute and late phase of beta-cell damage.[13] A preclinical animal study showed a relative insulin deficiency in rats following 5-FU administration, as well as a decrease in secretory granules of the pancreatic islet cells.[14] Furthermore,a retrospective study of 362 patients receiving 5-FU-based chemotherapies demonstrated long-term progressive C-peptide changes, including initial reduced early phase secretion and delayed peak, in which only 16% of patients who developed hyperglycaemic to diabetic levels had spontaneous normalisation of glycaemic levels; suggesting that 5-FU-induced injuries could result in permanent beta cell damage and subsequent sustained hyperglycaemic.[13]

In our case, the relationship of capecitabine and the patient's hyperglycaemic state was assessed using the Naranjo's adverse drug reaction (ADR) probability, a validated questionnaire for determining the likelihood of an ADR.[15] Hyperglycaemic was concluded to be a probable ADR of capecitabine, scoring a 5 based on previous reports on this reaction, hyperglycaemic appearing after capecitabine administration, hyperglycaemic confirmed with both elevated random blood glucose and elevated HbA1C and subsequent improvement of hyperglycaemic after suspension of capecitabine.[15] A probable ADR is described as a reaction that has previously been recognised by the suspected drug, has a reasonable temporal relationship following the suspected drug exposure and cannot be otherwise explained by

the patient's clinical status.[15] Consideration was given to possible metastatic lesions to the pancreas from the breast primary leading to altered glucose metabolism. However, metastatic lesions to the pancreas are rare in general, and typically arise from renal cell carcinoma, non-small cell lung cancers or colon cancers.[16] Breast cancer accounts for less than 5% of all metastatic pancreatic lesions.[16] CT scans both prior to and during the patient's hospitalisation did not reveal any focal pancreatic lesions, arguing against this theory. Furthermore, the patient was able to wean down her insulin requirements under the close monitoring of her family doctor following discharge and discontinuation of capecitabine.

Given that capecitabine is a generally well-tolerated chemotherapeutic agent with increasing indications for its use, it is important for clinicians to recognise its link to hyperglycaemic. In addition to routine monitoring of a patient's complete blood count, hepatic and renal function, clinicians should also regularly monitor blood glucose and lipid panel during capecitabine treatment and treat accordingly to guidelines. In this case, the patient presented in a decompensated state and as such, was initiated on an insulin regimen. However, if the patient had presented to her family doctor with new-onset diabetes without metabolic decompensation, it may have been reasonable to initiate a non-pharmacological approach and subsequent initiation on oral hypoglycaemic agents as per the 2018 Diabetes Canada Guidelines.[17]

Learning points

- Hyperglycaemic is a rare but important adverse effect of capecitabine therapy.
- Clinicians should consider monitoring blood glucose levels while a patient is on capecitabine therapy.
- Hyperglycaemic with metabolic decompensation should be initiated on insulin therapy.
- Hyperglycaemic can be persistent after cessation of capecitabine therapy.

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