CASE REPORT

Hypertriglyceridaemia-induced pancreatitis: a contributory role of capecitabine?

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Capecitabine is an orally administered pro-drug of 5-fluorouracil that confers superior disease-free survival and presumably has a more favourable side-effect profile. Here we report on a patient who developed acute necrotising pancreatitis and very high triglyceride levels as well as hand-foot syndrome after receiving capecitabine for colonic cancer. Increased awareness of this potential side-effect and close monitoring of lipid levels may be warranted, especially in patients who have other conditions predisposing them to severe secondary hyperlipidaemia when using this drug.

Case report

On 20 February 2010, a 42-year-old woman was admitted because of sudden onset of severe epigastric pain, repeated vomiting and passage of loose stool. She was a non-drinker. She had a history of fatty liver and gestational diabetes in 2002 (fasting blood glucose, 7.0 mmol/L; 2 hours after 75-g oral glucose, 12 mmol/L) requiring dietary control. In September 2009, Dukes' C adenocarcinoma of colon (pT3N1) was treated with right hemicolectomy, followed by adjuvant oral chemotherapy with capecitabine since October 2009. Each cycle of capecitabine lasted for 14 days followed by a 1-week drug holiday. After the first cycle of capecitabine, she complained of painful fingers and toes, compatible with grade-1 hand-foot syndrome. After receiving the second course of capecitabine, the toe pain was so severe that she had difficulty in walking, so the third course was postponed for 2 weeks and the dose of capecitabine reduced from 2000 mg twice daily to 1500 mg twice daily. The last (5th) course of capecitabine before admission was started on 5 February 2010 and stopped on 18 February 2010, 2 days before admission. There was no history of similar attacks or weight loss before this episode. She had not taken any other medications.

On physical examination, she was afebrile. Her body weight was 51.1 kg, height 1.54 m, and body mass index 21.5 kg/m^2. She did not have jaundice, pallor, or cyanosis. Her blood pressure was 139/73 mm Hg, and her pulse rate was 80 beats/min. Abdominal examination revealed generalised abdominal tenderness with voluntary guarding. There was no rebound tenderness. Bowel sounds were normal. Per rectum examination was unremarkable. She had no xanthoma or xanthelasma.

Laboratory findings of the patient are shown in the Table. The blood samples looked turbid. Lipid profile revealed gross elevations of triglyceride and cholesterol. Spot urine showed trace of albumin only. Chest X-ray did not show any free gas under diaphragm. Abdominal X-ray showed faecal-loaded bowel loops without signs of intestinal obstruction. An urgent computed tomographic abdomen revealed pancreatic necrosis, an ill-defined pancreatic outline with a peri-pancreatic collection and splenic thrombosis. The diagnosis of acute necrotising pancreatitis was made based on the clinical, radiological, and laboratory findings.

The patient was transferred to the intensive care unit. Despite fluid challenge, in the course of the illness she developed fever, sinus tachycardia, and oliguria and septic shock. The Ranson scores on admission and at 48 hours were 2 and 7, respectively. She was sedated with a propofol infusion and treated with insulin, noradrenaline, mechanical ventilation, percutaneous drainage of the peri-pancreatic collection, two sessions of plasmapheresis and total parenteral nutrition. Her lipaemic index was normalised after the first session of plasmapheresis. Gemfibrozil was started after the second session to maintain the lipid levels. She regained haemodynamic stability and her abdominal collections diminished in size after 3 weeks of intensive care. After the acute episode, however, she underwent three subsequent pancreatic necrosectomies to drain residual peri-pancreatic collections. Gemfibrozil was stopped 2 months later, with no recurrence of hyperlipidaemia. The patient's glycated haemoglobin ($HbA1_c$) was maintained at 6.9% with metformin 250 mg thrice a day. Her lipaemic index profile in relation to the time course of capecitabine and treatment is shown in the Figure.

Key words
Fluorouracil; Hand-foot syndrome; Hypertriglyceridemia; Pancreatitis; Plasmapheresis

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Discussion

Acute pancreatitis is one of the most feared consequences of severe hypertriglyceridaemia, which can be familial (Fredrickson types I, IV, and V) or secondary to a number of other causes. Hypertriglyceridaemia can also be due to a combination of primary and secondary causes.

While our patient's hyperlipidaemia could have been partially accounted for by insulin resistance, as exemplified in diabetic patients with a fatty liver, her very high triglyceride levels seemed to be disproportionate to her diabetes mellitus. This led us to suspect an additional role of capecitabine. She

高甘油三脂血症誘發胰腺炎：卡培他濱片的副作用

卡培他濱片（capecitabine）是氟尿嘧啶（5-fluorouracil）的口服藥物，有極佳的無疾病存活率，而且副作用應較少。本文報告一名結腸癌患者服食卡培他濱片後出現急性壞死性胰腺炎。患者的甘油三脂水平亦非常高，並出現手足綜合徵。要留意病人服食卡培他濱片後有否出現此等副作用，並密切監察病人的血脂水平，尤其是如果病人的其他情況有可能產生嚴重的繼發性高脂血症時，便需格外留意。

TABLE 1. Laboratory findings of the patient

Laboratory finding	Patient's level	Reference range/level
Haemoglobin (g/L)	134	134-171
White cell count (x 10^9 /L)	16.4	3.7-9.2
Platelet (x 10^9 /L)	113	145-370
Plasma sodium (mmol/L)	127	136-145
Potassium (mmol/L)	3.8	3.4-5.0
Urea (mmol/L)	4.6	3.0-7.4
Creatinine (μmol/L)	68	65-110
Albumin (g/L)	37	35-52
Total bilirubin (μmol/L)	3	5-27
Alkaline phosphatase (IU/L)	114	34-97
Alanine transferase (IU/L)	35	8-36
Amylase (IU/L)	2046	27-131
Total calcium (mmol/L)	1.60	2.10-2.62
Ionised calcium (mmol/L)	0.99	1.13-1.32
Phosphate (mmol/L)	1.31	1.03-1.57
Lactate dehydrogenase (IU/L)	343	27-131
International normalised ratio	1.08	-
Lactate (mmol/L)	7.6	0.5-2.2
β-Hydroxybutyrate (mmol/L)	0.28	<0.27
C-reactive protein (mg/L)	44.6	<5.0
Spot glucose (mmol/L)	19.8	<6.1
Glycated haemoglobin (%)	10.7*	4.8-6.0
Thyroid-stimulating hormone (mIU/L)	2.19	0.27-4.20
pH	7.30	7.35-7.45
Partial pressure of carbon dioxide (kPa)	4.3	4.7-6.0
Partial pressure of oxygen (kPa)	13.2	10.0-13.3
Base excess (mmol/L)	-9.6	-2.0 to 2.0
Bicarbonate (mmol/L)	16	22-26
Oxygen saturation (%)	97	95-98
Triglyceride (mmol/L)	111.2	<1.7
Cholesterol (mmol/L)	32.1	<5.2
High-density lipoprotein cholesterol (mmol/L)	2.2	<1.0

* Last measured in 2002: 6.0%

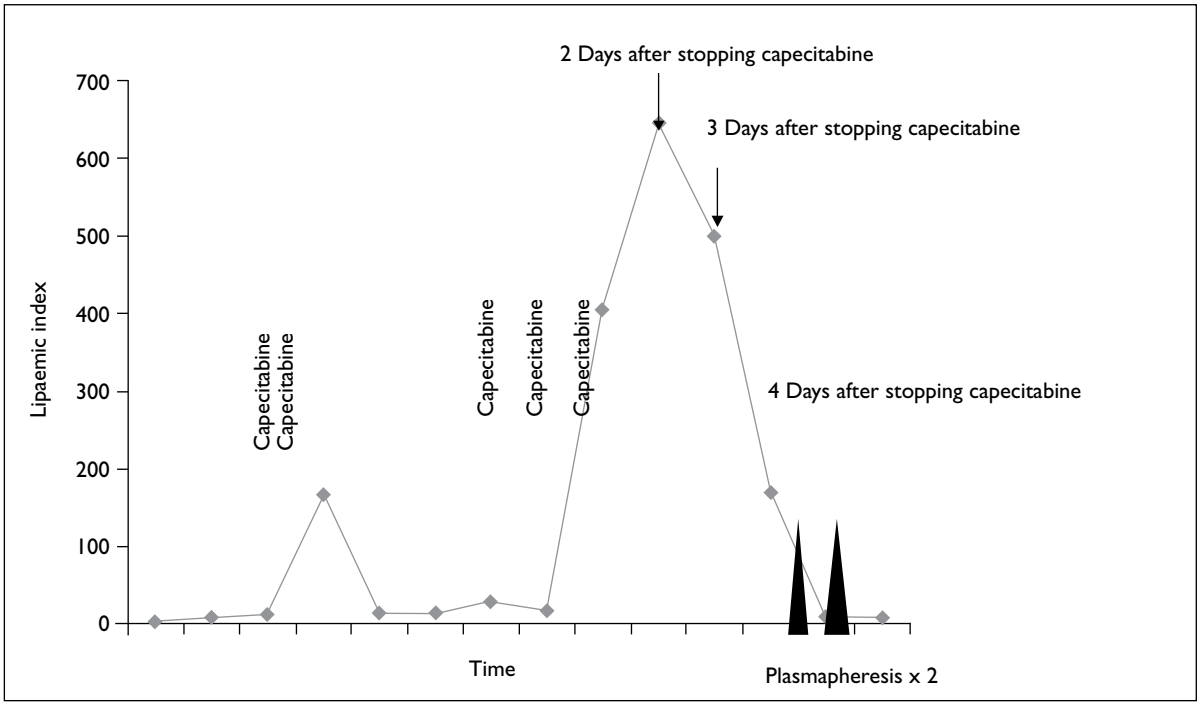

FIG . The trend of lipaemic index after using and stopping capecitabine

had no other risk factors such as alcoholism, obesity, thyroid disorder, renal disease, or intake of other suspect medications. The full recovery of her lipid profile after withdrawal of capecitabine and control of diabetes mellitus, as well as the absence of features of familial hyperlipidaemia (eruptive xanthoma, lipaemic retinalis or hepatosplenomegaly), were also inconsistent with a strong genetic predisposition.

Capecitabine is an orally administered pro-drug of 5-fluorouracil that achieves superior disease-free survival and presumably confers a more favourable side-effect profile. Nowadays, it is commonly used as adjuvant treatment of colorectal cancer and metastatic breast, gastric or colon cancer, especially in out-patient settings. Capecitabine has been documented to be associated with hypertriglyceridaemia.[1] In the early days of its use, it was thought to cause hypertriglyceridaemia in only 0.1 to 1% of patients.[2] More recent reports suggested that this complication occurs more frequently, in 3.7 to 10% of patients taking the drug.[3,4] Severe capecitabine-induced hypertriglyceridaemia had also been reported, with levels between 10.4 and 35.2 mmol/L,[2,5-7] and pancreatitis had been documented to occur in some of these patients.[8,9] It is not known whether the triglyceride level is related to the dose of capecitabine, or whether certain individuals are more prone. Apart from pancreatitis, in our patient capecitabine also induced the hand-foot syndrome. This combination of adverse effects has also been reported.[8] How hand-foot syndrome is induced is not known however, and whether it could be a premonitory signal for hypertriglyceridaemia is also unclear.

The exact mechanism of capecitabine-induced hypertriglyceridaemia remains enigmatic. Since hypertriglyceridaemia had not been reported with 5-fluorourail, it is postulated that capecitabine itself or metabolites produced en route of its transformation into 5-fluorouracil (eg 5′-deoxy-5-fluorocytidine or 5′-deoxy-5-fluorouridine) are responsible for this complication. It has also been suggested that capecitabine may reduce the activity of lipoprotein lipase and hepatic triglyceride lipase.[1] Garg et al[7] reported that capecitabine might induce diabetes, but in other reported cases the development of diabetes mellitus did not appear to be a prerequisite for hypertriglyceridaemia.[3,5,6,8] We do not know whether or not the severity of the diabetes mellitus in our patient was related to capecitabine. After the acute episode her $HbA1_c$ was reduced by 3.8% with metformin, a drug that had been reported to reduce $HbA1_c$ by 1 to 2% in diabetic patients.[10]

In our patient, there was no prior available sample before this episode for retrospective lipid analysis to further explore whether capecitabine administration might have caused hypertriglyceridaemia. We therefore analysed the lipaemic index of previous blood samples to determine whether there was any temporal relationship between this parameter and capecitabine administration. The lipaemic index

is a measure of light scatter which is automatically captured by all laboratory analyses that provide an estimate of sample turbidity.[11] It is affected by both the concentration of triglyceride and the size of the lipoprotein particle,[12,13] so it can be used as a surrogate marker for the degree of hyperlipidaemia. Before the initiation of capecitabine, her lipaemic indices were normal and stable at around 15. Eight days after the initiation of the second course of capecitabine, her non-fasting blood sample appeared grossly turbid and the lipaemic index was elevated up to 165. It dropped spontaneously 1 week later, when capecitabine had been stopped for 7 days. The third and fourth courses of capecitabine, given at reduced doses and at delayed intervals after the second course, were not associated with changes in lipaemic index. At the time of pancreatitis, 2 days after the last dose of the fifth course of capecitabine, the lipaemic index was again elevated to 646. We cannot definitively conclude from this pattern a contributory role for capecitabine in this patient's hypertriglyceridaemia, although it appears to be plausible. Although the rise in lipaemic index was rather abrupt and may occur only at a cumulative threshold dose of capecitabine, it is not yet established that close monitoring of lipid levels can prevent such life-threatening acute pancreatitis. We nevertheless recommend checking baseline lipid levels and monitoring them closely when using this drug. This may enable us to collect more information on the relationship between this drug and hypertriglyceridaemia. In patients with severe hypertriglyceridaemia, it is important to be aware of several management caveats. High triglyceride levels can cause assay interference, leading to false elevations in haemoglucostix, blood glucose and $HbA1_c$; they may also cause pseudohyponatraemia. To minimise such interference, before analysis, samples should be vigorously centrifuged using high-speed micro-centrifuges or treated with lipid clearing agents. Propofol should also be used with caution, since it too is associated with hypertriglyceridaemic acute pancreatitis.[14]

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