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5-Fluorouracil-associated severe hypertriglyceridaemia with positive rechallenge

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Accepted 17 November 2023

To cite: Giacomuzzi Moore B, Durigova A, Lamine F, *et al*. *BMJ Case Rep* 2023;**16**:e254871. doi:10.1136/bcr-2023-254871

SUMMARY

Chemotherapy-induced hypertriglyceridaemia (HTG) is a potential serious adverse event. Severe HTG with triglycerides (TG) >11.3 mmol/L (1000 mg/dL) can cause acute pancreatitis in addition to cardiovascular diseases such as coronary artery disease. While the association of capecitabine (5-fluorouracil (5-FU) prodrug) with clinically relevant HTG is a well-known adverse reaction, 5-FU is not typically associated with HTG. We here report the case of a patient who developed 5-FU-associated grade 4 HTG with TG level raising up to 37.1 mmol/L (3286 mg/dL) occurring after the ninth cycle of adjuvant FOLFOX (Fluorouracil and Oxaliplatin) chemotherapy. Fenofibrate treatment and diet were started. Chemotherapy was postponed and then resumed for two additional cycles. However, severe HTG recurred shortly after. Chemotherapy was therefore permanently stopped. Approximately 8 weeks after chemotherapy discontinuation, TG fell back to range at 2.1 mmol/L (189 mg/dL) allowing interruption of fenofibrate without HTG recurrence at 3 months.

BACKGROUND

5-Fluorouracil (5-FU) is a common chemotherapeutic agent that has long been established in the treatment of various cancers, especially colorectal cancer (CRC), in the neoadjuvant, adjuvant and metastatic setting. Commonly reported adverse reactions of this treatment are asthenia and haematotoxicity and gastrointestinal (GI) disorders such as nausea, vomiting and diarrhoea. HTG is not classically documented in association with 5-FU therapy.

Clinically relevant HTG has been recognised as a well-known adverse side effect of capecitabine (a prodrug of 5-FU) with a prevalence of around 3.4%.[1–6] Differently, 5-FU is not classically associated with HTG. A single case report in literature describes intravenous 5-FU-induced mildly severe HTG, in a patient who had previously experienced capecitabine-induced HTG before starting 5-FU intravenous treatment.[7] The same side effect was reported in correlation to S-1, an oral fluoropyrimidine that consists of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate.[8]

We here report an unusual case of intravenous 5-FU-associated severe HTG in a fluoropyrimidine naïve patient with stage IIIC colon cancer and hypothesise on the possible pathophysiological mechanism of such a side effect, possibly implying dysregulation of mitochondrial function and/or peroxisome proliferator-activated receptor (PPAR)-α, crucial to hepatic lipid metabolism.

CASE PRESENTATION

Our patient was a man in his early 50s, with no known medical comorbidities and no known dyslipidaemia or type 2 diabetes. He was overweight (BMI 29.9 kg/m^2). His family history was unremarkable for cardiovascular or endocrine disorders. He did not smoke and his alcohol consumption was occasional. Blood workup was within range values before chemotherapy, including TG level. Total cholesterol, high-density lipoprotein cholesterol (HDLc) and low-density lipoprotein cholesterol (LDLc) were not measured. He was not taking any chronic medication.

He was diagnosed with colon cancer, more precisely with mucinous adenocarcinoma of the left colon stage pT4a pN2a (5/22) cM0, stage IIIC, MSS/pMMR. The patient underwent surgery for left hemicolectomy. Given the IIIC staging after R0 surgery, adjuvant chemotherapy was recommended. FOLFOX adjuvant chemotherapy (5-FU 400 mg/m^2 bolus day 1, 5-FU 2400 mg/m^2 infusion over 48 hours day 1–2, leucovorin 200 mg/m^2 day 1, oxaliplatin 85 mg/m^2 day 1—every 2 weeks) was started for what were planned to be 12 complete cycles of treatment. The patient presented no adverse reactions except for grade 1 polyneuropathy starting after the fifth cycle of chemotherapy.

After 16 weeks (at cycle 9 day 2 of chemotherapy), a deep vein thrombosis of the right axillary vein was diagnosed, and therapeutic anticoagulation with low molecular weight heparin treatment (LMWH) once a day was started for a duration of 3 months.

Three weeks later on blood testing before administrating the 10th cycle, our laboratory noticed a frankly lipaemic blood sample despite fasting state, which made the electrolyte and hepatic tests impossible to analyse. On double check on a second sample, the same issue occurred.

INVESTIGATIONS

After centrifugation, the blood showed a clear fatty supernatant (figure 1). The whole lipid panel was then measured revealing a severe grade 4 HTG (TG of 37.1 mmol/L (3286 mg/dL), with cholesterol value of 13.3 mmol/L (514.3 mg/dL), LDL value of 1.90 mmol/L (73.47 mg/dL) and HDL value of 0.50 mmol/L (19.3 mg/dL)).

No diabetes, thyroid function abnormality or renal impairment were found. No signs of

Figure 1 The appearance of a centrifuged plasma sample showing a milky supernatant.

pancreatitis were present. Clinical examination did not find cutaneous xanthomas.

DIFFERENTIAL DIAGNOSIS

Given that the initial TG level was near to normal before chemotherapy, that both secondary metabolic causes and analytical issues were ruled out and that neither oxaliplatin, leucovorin nor LMWH is known to induce HTG, 5-FU-associated HTG was first suspected.

TREATMENT

The 10th FOLFOX cycle was postponed. After endocrinological assessment, the patient was hospitalised for intravenous hydration, treatment with fenofibrate (200 mg one time per day) and low-carbohydrate low-fat diet were started. After 48 hours, TG decreased to 14.7 mmol/L (1300 mg/dL). The patient was discharged under fenofibrate treatment of 200 mg one time per day and a strict diet.

Ten days later, TG further decreased to 12.4 mmol/L (1105 mg/dL), allowing the administration of the 10th cycle of FOLFOX. A close follow-up of fasting serum lipid profile was performed at 1 and 2 weeks after the infusion and showed TG level rising again to 15.8 mmol/L (1404 mg/dL) and 20.8 mmol/L (1894 mg/dL), respectively, despite ongoing fenofibrate therapy. FOLFOX was therefore temporarily withheld. The 11th cycle of chemotherapy was administered with a 1-week delay when TG decreased to 8.7 mmol/L (771 mg/dL).

One week after this 11th cycle, TG raised again to 18.2 mmol/L (1616 mg/dL). FOLFOX was definitively stopped at the 11th cycle since the benefit-risk balance of continuing chemotherapy was judged unfavourable. Fenofibrate treatment of 200 mg one time per day was pursued.

OUTCOME AND FOLLOW-UP

The lipid profile was further controlled until TG returned to the level of 2.4 mmol/L (224 mg/dL) at 8 weeks from the last cycle of 5-FU chemotherapy (figure 2). Fenofibrate treatment was safely interrupted, and TG level remained stable (2.0 mmol/L) 3 months later.

DISCUSSION

We observed starting from the ninth FOLFOX cycle a severe increase in TG levels that could expose the patient to a substantial risk of acute pancreatitis.[9] The kinetics of TG fluctuations being closely correlated to FOLFOX challenge-dechallenge-rechallenge supported FOLFOX causality in HTG occurrence. This suspicion became most probable after ruling out alcohol abuse and other conditions such as diabetes, hypothyroidism and renal diseases. Since oxaliplatin is not classically associated with dyslipidaemia and since capecitabine and tegafur, two 5-FU prodrugs, are documented for the occurrence of HTG, 5-FU represented the main substance to be suspected in this TG elevation.

Our case raises concerns about the possible underestimation of HTG in cancer patients receiving 5-FU, considering that monitoring the lipid profile is not part of the usual recommended follow-up in cancer patients undergoing 5-FU-containing regimens.

Despite its widespread prescription, literature data on the impact of 5-FU on lipid profile in cancer patients is scarce. Our literature research showed that 5-FU can interfere with lipid metabolism.[10] A retrospective analysis of data from a cohort of CRC patients demonstrated an increase in total cholesterol, TG, HDLc and ApoA-1 levels in the group that received fluoropyrimidine-based chemotherapy.[11] We retrieved one single case of moderately severe HTG after the 13th cycle of 5-FU in a patient with stage IV rectal cancer. Bezafibrate was initiated, and 5-FU continued for

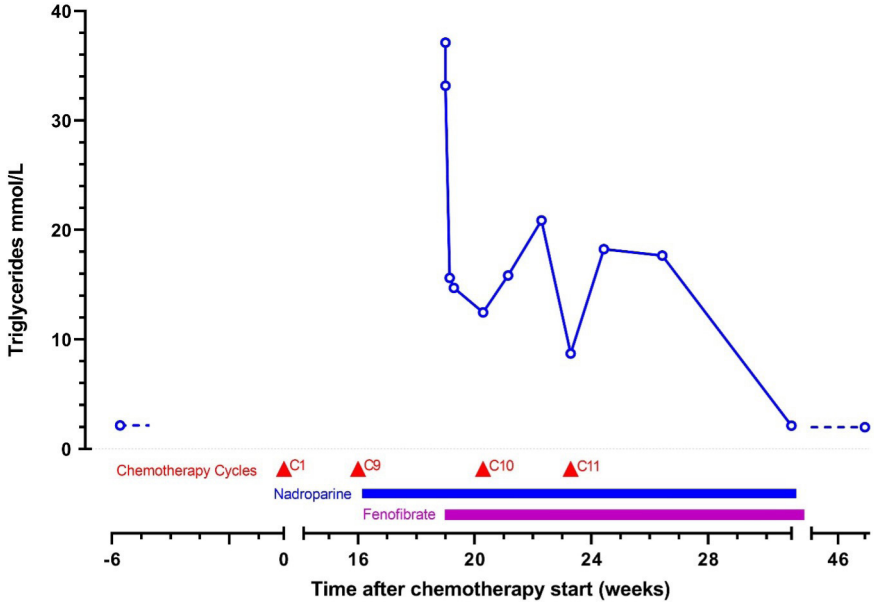

Figure 2 Triglyceride levels over time.

12 additional cycles with normalisation of TG. This patient was priorily exposed to CapeOx that induced moderate HTG, which resolved after treatment interruption.[7]

The pathophysiological mechanism of 5-FU-associated HTG is still poorly understood. Most available data are from studies that investigated the impact of 5-FU on the liver and especially 5-FU-associated steatohepatitis in patients with metastatic colorectal cancer. According to these data, incubation of HepG2 cells and human hepatocytes in the presence of 5-FU induces hepatic free fatty acids and TG accumulation possibly via dysregulation of mitochondrial function.[12] The discrepancy between capecitabine and 5-FU-induced HTG suggests that the effect could be related to capecitabine itself or to its intermediate metabolites, rather than to 5-FU itself. Observations of HTG with another 5-FU prodrug, tegafur, could also support this hypothesis.[13 14]

Individual predisposing factors could also favour such an impact on TG profile. The implication of other genes regulating lipid metabolism could also be questioned. PPAR-α, known to have a key role in the regulation of cancer cells,[15] is a nuclear receptor that increases expression of lipoprotein lipase (LPL), apoAI and other lipid-related genes, and it is the molecular target of fibrates. Doxorubicin was shown to cause downregulation of PPARγ and its cofactor liver X receptor α (LXRα), leading to lipoprotein increase and HDL decrease in breast cancer patients.[11] To our knowledge, there is no data on potential effects of fluoropyrimidine-based chemotherapy on PPAR-α gene expression.

The involvement of LMWH in HTG could be a contributing factor in our case. HTG was discovered 2 weeks after LMWH initiation, and TG level did not lower despite fenofibrate treatment, while LMWH was ongoing. Literature mentions that LMWH combined with insulin is empirically used as the first-line TG-lowering therapy in early-stage HTG-induced pancreatitis.[16 17] Concerning the possible mechanism of action, heparin acutely releases endothelial bound lipoprotein lipase LPL into the circulation and may reduce TG levels since LPL is the key enzyme involved in the intravascular hydrolysis of TG in circulating TG-rich lipoproteins.[18] However, according to Weintraub *et al*, continuous intravenous heparin administration decreased LPL activity along with an increase in circulating chylomicrons due to enhanced destruction of LPL by liver heparinase.[19]

Our protocol did involve deferring FOLFOX and subsequent rechallenge, while the patient was treated with fibrates and diet. A prospective study to assess the incidence of severe HTG during capecitabine treatment showed that continuing chemotherapy while providing introduction of fibrates and diet was effective and safe in the patients with grade 4 HTG.[5]

Learning points

- Although HTG is listed among the known adverse reactions of capecitabine, 5-FU-associated HTG is poorly documented.
- Our report provides strong arguments for suspecting the involvement of this chemotherapy in the observed severe TG elevation. The exact mechanism is not clearly identified. We could hypothesise that individual predisposing factors and a possible involvement of LMWH comedication may have elicited such an adverse reaction.
- From a clinical practice perspective, targeted lipid profile screening in high-risk patients starting 5-FU or 5-FU precursor treatments could be considered, providing a predefined management protocol for severe HTG in this setting and a close multidisciplinary management.

Contributors The following authors were responsible for drafting of the text, sourcing and editing of clinical images, investigation results, drawing original diagrams and algorithms and critical revision for important intellectual content: BGM, AD, FL, HC and ES. The following authors gave final approval of the manuscript: BGM, AD, FL, HC and ES.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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