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Case Report

Hypertriglyceridemia Induced by Fluorouracil: A Novel Case Report

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Keywords
Hypertriglyceridemia · Fluorouracil · Triglyceride · Fluoropyrimidine · Capecitabine

Abstract
We had previously reported on S-1-induced hypertriglyceridemia. Here, we report fluorouracil-induced hypertriglyceridemia in a patient with capecitabine-induced hypertriglyceridemia and the corresponding therapeutic process. A woman in her forties who had experienced grade 3 hypertriglyceridemia due to oxaliplatin + capecitabine was administered fluorouracil ± oxaliplatin + levofolinate calcium + panitumumab; however, grade 4 hypertriglyceridemia occurred after the thirteenth administration. Bezafibrate normalized the elevation. Chemotherapy cessation resulted in its decrease to normal, and bezafibrate was stopped. Nine months after cessation, treatment with fluorouracil + irinotecan + levofolinate calcium + ramucirumab was initiated. After four cycles of treatment, her serum triglyceride levels increased again to grade 3, and then, fenofibrate was administered, resulting in a significant decrease to grade 1–2. Serum triglyceride levels significantly reduced after cessation of the prior fluorouracil-containing regimen, although its elevation was observed again following the latter treatment. Therefore, fluorouracil-induced hypertriglyceridemia was strongly speculated in this case. We have speculated that the most probable cause of tegafur and capecitabine-induced hypertriglyceridemia is fluorouracil or its metabolic enzymes since their end product is fluorouracil in the previous report. Results from this patient suggest that our supposition was correct. Fibrates administration, cessation of the treatment, and monitoring of serum triglyceride level was effective in this case as well as previous reports. Fluorouracil-

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induced hypertriglyceridemia is associated with the one caused by tegafur and capecitabine and presents the possibility of severe complications. Elucidation of its exact mechanism and epidemiological features is needed for better understanding.

Introduction

We had previously reported on S-1-induced hypertriglyceridemia [1]. Here, we report fluorouracil-induced hypertriglyceridemia in a colorectal cancer (CRC) patient with capecitabine-induced hypertriglyceridemia, and the measures taken to treat it.

Case Presentation

A woman in her forties without hyperlipidemia had been administered CapeOX (oxaliplatin 130 mg/m^2 on day 1 along with capecitabine 2,000 mg/m^2/day on days 1–14, every 3 weeks) for stage IV rectal cancer, which resulted in grade 3 hypertriglyceridemia (serum triglyceride level, 518 mg/dL) after the fifth administration (Fig. 1). Consequently, the treatment was discontinued, and her triglyceride level decreased without further treatment to grade 1 (around 200 mg/dL). About 6 months later, treatment with mFOLFOX6 (fluorouracil 400 mg/m^2 on day 1 and 2,400 mg/m^2 for 46 h from day 1, oxaliplatin 85 mg/m^2 on day 1, and levofolinate calcium 200 mg/m^2 on day 1, every 2 weeks) and panitumumab (6 mg/kg, every 2 weeks) was initiated. Oxaliplatin was discontinued after the third administration due to hypersensitivity, whereas fluorouracil + levofolinate calcium (sLV+5FU2) + panitumumab were continued. Grade 3 hypertriglyceridemia (serum triglyceride level, 533 mg/dL) manifested after the seventh administration, which further developed to grade 4 hypertriglyceridemia (1,254 mg/dL) after the thirteenth administration. Sustained-release bezafibrate 200 mg twice a day was administered from the fourteenth administration, attenuating the elevation to normal level. Chemotherapy was discontinued after the twenty-sixth cycle, and we followed a wait-and-see approach without any chemotherapy. This resulted in a decrease in serum triglyceride levels to normal, and bezafibrate administration was stopped. Intrapelvic and lymph node recurrence was observed 9 months after cessation, and treatment with FOLFIRI (fluorouracil 400 mg/m^2 on day 1 and 2,400 mg/m^2 for 46 h from day 1, irinotecan 150 mg/m^2 on day 1, and levofolinate calcium 200 mg/m^2 on day 1, every 2 weeks) + ramucirumab (8 mg/kg, every 2 weeks) was initiated. After four cycles of treatment, her serum triglyceride levels increased again to grade 3 (676 mg/dL), and then, fenofibrate 160 mg once a day was administered, resulting in a significant decrease to grade 1–2. The patient experienced grade 2 nausea, anorexia, and fatigue during fluorouracil-containing regimens, and grade 2–3 skin toxicity during the former regimen. This patient had normal liver and renal function during the treatment, and supportive care was similar in both fluorouracil-containing regimens; palonosetron 0.75 mg on day 1, aprepitant (125 mg on day 1 and 80 mg on days 2 and 3), dexamethasone 9.9 mg infusion on day 1, 8 mg orally on days 2 and 3, and domperidone 10 mg three times a day from day 1 to nausea disappearance. The regular medication was mirabegron 25 mg twice a day, urapidil 15 mg twice a day, sustained-release tramadol 200–300 mg once a day, and vonoprazan 10 mg once a day during both fluorouracil-containing treatments. However, there were differences in the regular medication between the two regimens. Minocycline 100 mg once a day was administered for the entire duration of the former regimen, while in the latter regimen, edoxaban 30 mg, started 7 months prior to the initiation of chemotherapy, was administered once a day, and azilsartan 20 mg was

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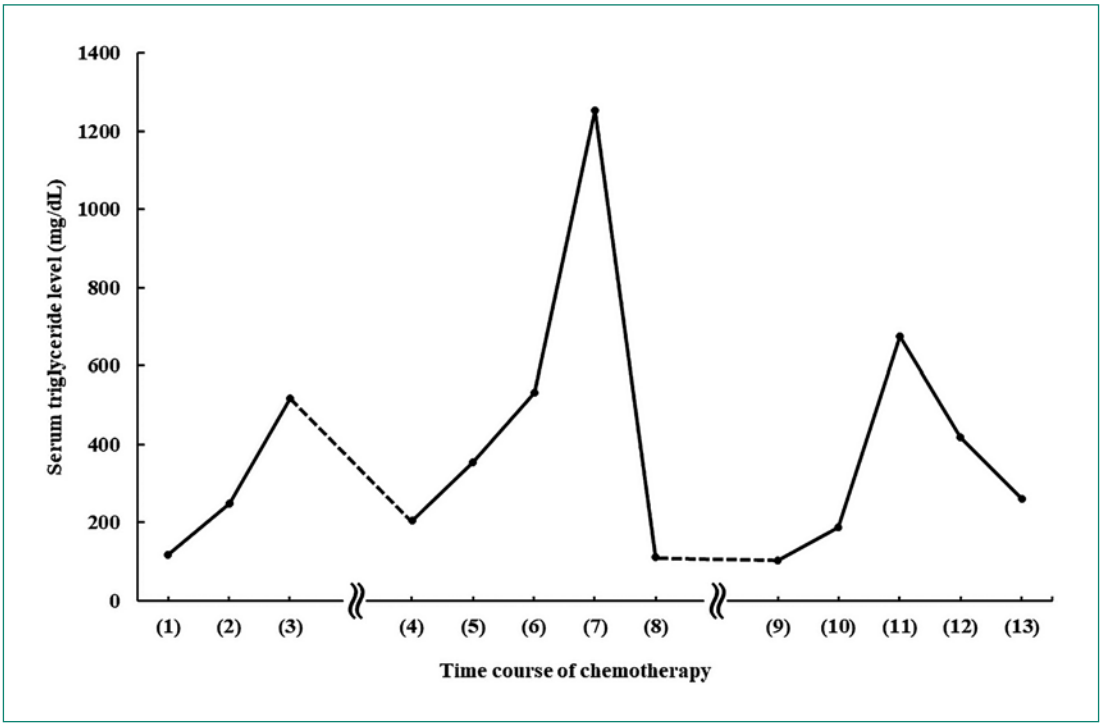

Fig. 1. Variations in the serum triglyceride level of the patient. (1) Baseline before CapeOX administration. (2) After fourth CapeOX administration. (3) After fifth CapeOX administration. (4) Baseline before mFOLFOX6 + panitumumab administration. (5) After fourth sLV+5FU2 + panitumumab administration. (6) After seventh sLV+5FU2 + panitumumab administration. (7) After thirteenth sLV+5FU2 + panitumumab administration. (8) After fourteenth sLV+5FU2 + panitumumab administration. (9) Two months after cessation of sLV+5FU2 + panitumumab administration. (10) Baseline before FOLFIRI + ramucirumab administration. (11) After fourth FOLFIRI + ramucirumab administration. (12) After eighth FOLFIRI + ramucirumab administration. (13) After twelfth FOLFIRI + ramucirumab administration. CapeOX: oxaliplatin + capecitabine; mFOLFOX6: fluorouracil + levofolinate calcium + oxaliplatin; sLV+5FU2: fluorouracil + levofolinate calcium; FOLFIRI: fluorouracil + levofolinate calcium + irinotecan.

administered once a day from the second cycle due to ramucirumab-induced hypertension. In summary, differences between the treatments were: (1) chemotherapy regimen and (2) regular administration of minocycline, edoxaban, and azilsartan.

Discussion

Chemotherapy is the first-line treatment for metastatic CRC, and pyrimidine fluoride agents belong to the most effective chemotherapeutic drugs in metastatic CRC treatment [2, 3]. We encountered a patient who had developed severe capecitabine-induced hypertriglyceridemia with both sLV+5FU2 + panitumumab and FOLFIRI + ramucirumab therapies. There are no reports regarding hypertriglyceridemia caused by oxaliplatin, irinotecan, levofolinate calcium, panitumumab, antiemetics, minocycline, and azilsartan. Edoxaban has been reported to induce hypertriglyceridemia (1.0%) [4]; however, as it was administered 7 months before FOLFIRI + ramucirumab treatment, the possibility for that is low. Ramucirumab has also been suggested to cause this adverse reaction, as shown in the RAISE study (0.9%) [5]; however, as it was co-administered with FOLFIRI, its involvement is unclear. Furthermore, as the

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patient experienced grade 2 nausea and anorexia in both treatments, it is speculated that her dietary triglyceride intake was poor. Thus, fluorouracil-induced hypertriglyceridemia was strongly indicated in this case and was evaluated using the Naranjo adverse drug reaction probability scale [6]. A score of 7, which is classified as "probable," was obtained (online suppl. Table 1, available at www.karger.com/doi/10.1159/000512820).

It is important to manage the risk of chemotherapy-induced hypertriglyceridemia since it may lead to vascular disease and acute pancreatitis [1]. We have reported S-1-induced, while others have reported capecitabine-induced hypertriglyceridemia [7–9]. In addition, there has been a report about a patient who had developed capecitabine-induced hypertriglyceridemia and also experienced tegafur/uracil-induced hypertriglyceridemia [10]. Even though the detailed mechanisms behind this are still unknown, we have proposed the hypothesis that tegafur, capecitabine, fluorouracil itself, or their metabolizing enzymes might have affected lipid metabolism [1]. Specifically, we have speculated that the most probable cause is fluorouracil or its metabolic enzymes since the end product of both tegafur and capecitabine is fluorouracil [1]. Results from this patient suggest that our supposition was correct. Therefore, it is necessary to elucidate the mechanism of fluorouracil-induced hypertriglyceridemia. Javot et al. [9] guessed that thymidine phosphorylase could play a role in inducing hypertriglyceridemia. It has been reported that thymidine phosphorylase and thymidine kinase compete for thymidine, resulting in catalysis of synthetic and catabolic reactions involving proliferation and angiogenesis [11]. It is also known that modification of the expression and activity of thymidine kinase as well as a strong increase in secretory phospholipase-A2 occur in resistant colon cancer cells [12]. These may explain a relationship between thymidine metabolic pathways and phospholipid metabolism, which might be a partial cause of fluorouracil-induced hypertriglyceridemia [1]. In addition, genetic factors influencing metabolic enzymes such as dihydropyrimidine dehydrogenase, thymidine phosphorylase, and pyrimidine nucleotide phospholylase might have contributed to the occurrence of this symptom.

Moreover, Michie et al. [7] have reported that capecitabine-induced hypertriglyceridemia occurs in 3.7% of patients receiving capecitabine-containing regimens, although the exact epidemiology is unknown. In addition to the mechanism, it is also important to understand the epidemiological features of this adverse effect in order to implement early detection and appropriate preventative treatment.

Fibrates significantly reduced the serum triglyceride level, which, in this case, was normalized after cessation of the treatment. These results are similar to those of previous reports on other fluoropyrimidines [1, 7–10] and support the recommendation regarding its management [1, 7, 8]. Results obtained in this and previous reports also suggest that observation at baseline and periodic assessment of lipid profiles are necessary in patients administering fluoropyrimidines [1, 7–10]. Notably, we strongly recommend monitoring patients with cardiovascular disease or at risk, such as those with hypertension, coronary heart disease, dyslipidemia, obesity, and diabetes [1, 9]. Interestingly, the serum triglyceride level did not return to normal after 6 months from the last CapeOX administration in this case, suggesting that monitoring is necessary after the cessation of the suspected drug for a certain period. As hypertriglyceridemia is non-symptomatic in most cases, we should be aware of its possible occurrence.

Conclusion

Hypertriglyceridemia caused by fluorouracil is associated with the one caused by tegafur and capecitabine and presents the possibility of severe complications. However, its exact mechanism and epidemiological features such as time and frequency of appearance and risk factor(s) are still unclear. Thus, further studies are needed for better understanding.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

Y.S., Y.T., S.Y., and M.S. have no conflicts of interest. Y.K. reports honoraria from Pfizer, Novartis, and Bayer; research funding from Eli Lilly, MSD, Ono Pharmaceutical, Novartis, Bayer, Chugai Pharma, Yakult, and Taiho; and provided speaker services for Eli Lilly, Chugai Pharma, Merck Serono, Novartis, Pfizer, Bayer, and Taiho.

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Author Contributions

Y.S. contributed the design of the report and collected the data, and drafted the manuscript. Y.T., S.Y., Y.K., and M.S. revised the manuscript. All authors have read and approved the final version of the manuscript.

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