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Case Report

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Capecitabine-induced Hypertriglyceridemia in a Patient with Gallbladder Adenocarcinoma

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Abstract

A 71-year-old man with gallbladder adenocarcinoma and no history of dyslipidemia presented with serum triglyceride level of 912 mg/dL after two months of starting Capecitabine. The lipemia due to elevated triglyceride also led to hemolysis, causing analytical interference to other biochemical tests and complete blood count.

Keywords: Capecitabine, Xeloda, Hypertriglyceridemia, Serum Triglyceride Levels, Drug Adverse Effect

Key Clinical Message

Capecitabine-induced hypertriglyceridemia is a rare adverse effect. When present, it can cause analytical interference to other blood tests and potentially lead to inaccurate results.

Introduction

Capecitabine (Xeloda) is an oral fluoropyrimidine most commonly used for the treatment of metastatic breast cancers and gastrointestinal cancers. Capecitabine is a prodrug which is metabolized to 5-deoxy-5-fluorocytidine and 5-deoxy-5-fluorouridine before conversion to the active 5-flurouracil (5-FU) [1]. Commonly reported adverse effects include diarrhea, plantar-palmar erythrodysesthesia, stomatitis, and nausea [2, 3]. Hypertriglyceridemia is a rare adverse effect cited to occur in 0.1 to 1 % of patients on this medication [4]. 5-FU is not known to cause hypertriglyceridemia. It may actually lower serum cholesterol and lipids. This may indicate that hypertriglyceridemia is due to the Capecitabine molecule itself or one of the intermediates preceding its final conversion to 5-FU [1]. Hypertriglyceridemia can potentially result in serious clinical consequences, especially for cancer patients because of a high incidence of comorbidities. Here we present a case of Capecitabine-induced hypertriglyceridemia that interfered with the measurement of multiple biochemistry laboratory tests and complete blood count.

Case Report

A 71-year-old African American man with no significant past medical history presented with abdominal pain and acute appendicitis. CT scan revealed an incidental gallbladder mass and he underwent radical cholecystectomy with liver resection and lymphadenectomy which demonstrated a poorly-differentiated adenocarcinoma of the gallbladder, measuring 2.5 cm and invading peri-muscular connective tissue without extension to the serosa of the liver. Two of four lymph nodes were positive for metastatic carcinoma, and his overall stage was IIIB (T2, N1, cM0). Approximately six weeks following surgery, he was started on adjuvant therapy with oral Capecitabine (1500 mg) and intravenous Gemcitabine (800 mg/m2) with four cycles planned, administered every twenty-one days, with radiation therapy. He tolerated the chemotherapy well, and after three cycles (two months after starting adjuvant therapy) laboratory testing of a basic metabolic panel, complete blood count (CBC), and liver enzymes was ordered for routine monitoring. The laboratory results for potassium, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and several CBC parameters could not be released due to lipemic and hemolytic interference. On inspection of the blood sample, it had a milky and pink appearance, so a subsequent blood draw was performed three hours after the first (Figure 1). Laboratory values of the subsequent blood draw mirrored the first, and the triglyceride concentration was measured to evaluate for lipemia as a cause of hemolysis (Table 1). The triglyceride level was found to be elevated at 912 mg/dL (normal <150 mg/dL) (Table 2). The triglyceride level two months prior to cholecystectomy was 108 mg/dL. Given the hypertriglyceridemia, Capecitabine was discontinued, and Gemcitabine was administered as monotherapy for the fourth cycle. No medication for dyslipidemia was administered. Within one month of stopping Capecitabine, the triglyceride concentration normalized to 168 mg/dL.

Table 1: Biochemistry Laboratory Results for the Initial Sample and the Sample Drawn After Three Hours.

	Blood Draw 1	Blood Draw 2
Glucose (mg/dL)	195	110
Sodium (mmol/L)	138	138
Potassium (mmol/L)	Not reported	Not reported
Chloride (mmol/L)	100	101
Bicarbonate (mmol/L)	23	23
BUN (mg/dL)	11	10
Creatinine (mg/dL)	1.1	1.1
Calcium (mg/dL)	9.3	9.6
Total Protein (g/dL)	7.5	7.6
Albumin (g/dL)	3.9	3.9
Total Bilirubin (mg/dL)	0.5	0.5
ALP (U/L)	Not reported	Not reported
AST (U/L)	Not reported	Not reported
ALT (U/L)	Not reported	Not reported
Triglyceride (mg/dL)	-	912
LDL (mg/dL)	-	40

Table 2: Cholesterol and triglyceride levels two months prior to cholecystectomy, after the third cycle of chemotherapy, and one month following the last administration of Capecitabine.

	Pretreatment	During Treatment	One Month After Stopping Treatment
Triglyceride (mg/dL)	108	912	168
LDL (mg/dL)	105	40	-
Hemolytic index	-	398	24
Lipemic index	-	142	20

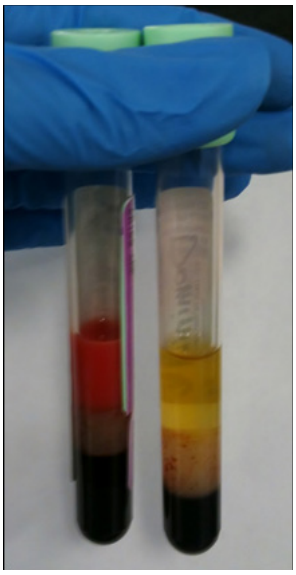

Figure 1: The patient's blood sample, submitted after the third cycle of chemotherapy, is shown alongside an unaffected patient's blood. Of note, the patient's sample demonstrates a milky and pink appearance, consistent with hypertriglyceridemia and hemolysis.

Discussion

Capecitabine-induced hypertriglyceridemia is a rare adverse effect with the potential for serious clinical consequences in the adjuvant chemotherapy setting. Acute pancreatitis can result from hypertriglyceridemia and in severe cases may be fatal. Cases of pancreatitis in patients while on Capecitabine had been reported [5].

Our patient presented with analytical interferences in laboratory results due to hemolysis and lipemia. In this case, severe hemolysis and lipemia prompted a visual inspection of the blood specimen, which revealed a milky pink appearance. Various studies have demonstrated an association between hypertriglyceridemia and hemolysis, however, the mechanism for this observation was not completely understood [6, 7]. It has been proposed that hypertriglyceridemia or hyperlipidemia may cause an alteration in erythrocyte membrane composition, resulting in increased fragility [6]. It may also be possible that hyperlipidemia results in lipid peroxidation of unsaturated fatty acids of the erythrocyte membrane which could induce hemolysis [7].

In our patient, the hypertriglyceridemia did not develop immediately after therapy but was found to occur three cycles (two months)

after the initiation of Capecitabine. This was consistent with other reports that showed the adverse effect two to eight cycles after the initiation of Capecitabine [2, 3, 8-16]. The mechanism for hypertriglyceridemia with Capecitabine use is currently not known. It had been suggested that Capecitabine may alter lipid metabolism by altering lipoprotein lipase and hepatic triglyceride lipase [15]. Another theory stated that Capecitabine may alter nucleic acid and phospholipid metabolism [16].

The hypertriglyceridemia in our patient resolved within one month following discontinuation of Capecitabine, and no therapy for dyslipidemia was required. In practice, Capecitabine need not be discontinued, and cases demonstrate successful continuation of the drug alongside lipid-lowering medication such as Fenofibrate [15-17]. This case had a score of +7 on the Naranjo adverse drug reaction probability scale, indicating probable drug reaction, because the hypertriglyceridemia appeared after Capecitabine was administered (+2); the hypertriglyceridemia improved when Capecitabine was discontinued (+1); the hypertriglyceridemia was confirmed by objective evidence (+1); there are previous conclusive reports on the reaction (+1); and there are no alternative causes (other drugs) that could have caused this reaction on their own (+2) [18].

The manufacturer's product information from Roche reports a 0.1 to 1% incidence of Grade 3 (five to ten-fold above the upper limit of normal) or Grade 4 (ten-fold increase) elevations in serum triglycerides with Capecitabine [4]. Some studies suggest that the true incidence may be higher than previously reported, and that some level of hypertriglyceridemia less than Grade 3 can also occur. Seminara and colleagues noted that out of thirty eight patients on Capecitabine-based regimens for breast and gastrointestinal cancers, two patients developed severe hypertriglyceridemia with triglyceride levels above 1,000 mg/dL and two others had serum triglyceride levels elevated to approximately 2.5 times pretreatment levels [12]. Michie and colleagues observed that 8 out of 212 patients treated with Capecitabine demonstrated clinically significant hypertriglyceridemia that normalized with lipid-lowering therapy [19]. Stathopoulos and colleagues noted that hypertriglyceridemia was observed in 5 of 12 patients on Capecitabine monotherapy for breast and colon cancer, and one patient had triglycerides elevated to 1100 mg/dL while the other four patients' triglyceride levels were elevated to three to four times the normal levels [15].

Conclusion

Capecitabine-induced hypertriglyceridemia is a rare adverse effect, but clinicians should be aware of its existence. In the reported case, the phenomenon was discovered after laboratory interferences of hemolysis and lipemia led to further laboratory work-up. At present, serum triglycerides are not routinely tested in patients undergoing treatment with Capecitabine and the true incidence of this adverse effect has yet to be thoroughly investigated.

Abbreviations

5-FU: 5-Fluorouracil
ALP: Alkaline Phosphatase
AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase
BUN: Blood Urea Nitrogen
CBC: Complete Blood Count
LDL: Low Density lipoprotein

Conflict of Interest

The authors declare that they have no conflict of interest to report.

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