Case report

Massive hypertriglyceridemia associated with paclitaxel; a case report

Anojian Koneshamoorthy a,*, Danielle Hulse a, Chia Yuen Chong b, Balasubramanian Krishnamurthy a,c, Sumitra Ananda b,d,e,f, Peter S. Hamblin a,f

a Department of Endocrinology and Diabetes, Western Health, Melbourne, Australia
b Department of Medical Oncology, Western Health, Melbourne, Australia
c St Vincent’s Institute of Medical Research, Melbourne, Victoria, Australia
d Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia
e Epworth Freemasons, East Melbourne, Australia
f Department of Medicine, Western Health, University of Melbourne, St Albans, Victoria, Australia

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ABSTRACT

This report describes a patient who developed massive hypertriglyceridemia (12,488 mg/dL or 141 mmol/L) during paclitaxel and carboplatin adjuvant chemotherapy for high grade serous fallopian tube carcinoma. Paclitaxel was thought to be the causative agent and she had normal triglyceride levels following a change to carboplatin and gemcitabine. To our knowledge, this is the highest reported triglyceride level associated with paclitaxel. Measurement of serum lipids should be considered in individuals receiving taxane chemotherapy, especially in those with type 2 diabetes mellitus or a history of dyslipidemia.

1. Introduction

Fallopian tube serous carcinomas are malignancies originating from the transformation of the salpingeal mucosa (Stasenko et al., 2019). The incidence is reported to be 0.36 to 0.41 per 100,000 women per year with a median age of 64 years (Stewart et al., 2007).

Given the similarities in clinical behaviour with ovarian, fallopian tube and peritoneal carcinomas, the treatment approach is the same (Stasenko et al., 2019). When optimal cytoreduction can be achieved, surgical debulking is recommended for stage III or IV disease, followed by adjuvant chemotherapy which is traditionally a platinum doublet of carboplatin and paclitaxel (Stasenko et al., 2019).

Hypertriglyceridemia is a common form of dyslipidemia (Brunzell, 2007). Several genetic disorders can cause hypertriglyceridemia including familial combined hyperlipidemia, residual dyslipidemia in persons with well controlled type 2 diabetes mellitus and familial hypoalphalipoproteinemia (Brunzell, 2007). Uncontrolled diabetes, alcohol consumption and treatment with several drugs can lead to secondary hypertriglyceridemia (Brunzell, 2007). Here we report a case of massive hypertriglyceridemia attributed to paclitaxel, utilised to treat high grade fallopian tube serous carcinoma.

2. Case presentation

A 71-year-old woman was diagnosed with a stage III high grade serous fallopian tube carcinoma with omental disease in September 2021, following a diagnostic laparoscopy with salpingectomy and omental biopsy. Immunostains where positive for p53, WT1, PAX 8, p16, CK7, ER (95%) and negative for calretinin and CK20. Her CA125 at diagnosis was 101 U/mL (0–35). She had a history of well controlled mixed dyslipidemia, and insulin-dependent type 2 diabetes for more than 20 years, (HbA1c was 7.1 % (54 mmol/mol) 13 days before the first chemotherapy cycle, indicating good diabetes control and historical HbA1c of 7.2% (55 mmol/mol) dating back to 2017).

She also had hypertension, untreated mild subclinical hypothyroidism, gastro-esophageal reflux disease, osteoporosis, depression and a past history of T8/T9 vertebral tuberculosis in 2017. Her medications were rosuvastatin 10 mg daily, telmisartan 40 mg daily, amlodipine 10 mg daily, escitalopram 20 mg daily, Ryzodeg® insulin (degludec/insulin aspart) twice daily, linagliptin 5 mg daily, metformin 1000 mg daily, alendronate 70 mg weekly and nizatidine 150 mg daily.

She received the first of three cycles of paclitaxel in cremophor EL (CrEL) excipient on 29th September 2021 at a dose of 313 mg (175 mg/m2) and carboplatin AUC 6 (691 mg). After the three cycles, the plan was for her to be assessed for suitability of surgical debulking, followed...
by a further three cycles of adjuvant chemotherapy. Dexamethasone was
administered in a dose of 12 mg intravenously on the day of chemo-
therapy, followed by 4 mg orally twice daily for the first two days
following chemotherapy. She experienced grade 1 painful peripheral
neuropathy following the first cycle, for which she was prescribed
gabapentin 300 mg daily.

Seventeen days after her third cycle of chemotherapy, she was inci-
dentially found to have massive hypertriglyceridemia with triglyceride
level of 12,488 mg/dL (141 mmol/L) and total cholesterol level of 1369
mg/dL (35.4 mmol/L) on blood testing arranged for a routine diabetes
clinic appointment. The laboratory urgently contacted the endocrinol-
ogist who had requested the blood test. The patient was then contacted
and reported that she felt well. She had no symptoms to suggest acute
pancreatitis.

There was no prior history of severe hyperlipidemia. She was
commenced on rosuvastatin 10 mg in 2017 with total cholesterol of 232
mg/dL (6.0 mmol/L) and triglycerides of 124 mg/dL (1.4 mmol/L).
Prior testing in 2010 demonstrated a normal lipid panel with total
cholesterol of 135 mg/dL (3.5 mmol/L) and 44 mg/dL (0.5 mmol/L).
She had no clinical signs of acanthosis nigricans or eruptive xanthomas.
Her most recent total cholesterol level prior to chemotherapy was 155
mg/dL (4.0 mmol/L) and triglyceride was 177 mg/dL (2.0 mmol/L), 13
days before her first cycle. Other investigations at the time of the severe
hypertriglyceridemia demonstrated deterioration of her diabetes control
with HbA1c of 8.9% (74 mmol/mol), with cyclical use of dexametha-
sone, and mild subclinical hypothyroidism with an elevated thyroid
stimulating hormone (TSH) of 6.13 mIU/L (0.5–4.0) but normal free
thyroxine (FT4) of 1.16 ng/dL or 14.9 pmol/L (0.78–1.79 ng/dL or
10–23 pmol/L). These thyroid function tests were similar to previous
levels in May 2021 (TSH 5.26 mIU/L, FT4 of 1.1 ng/dL or 13.7 pmol/L).

The incidental discovery of massive hypertriglyceridemia raised
concerns for the potential development of severe pancreatitis. Serum
lipase was measured urgently and fortunately was found to be only
minimally elevated at 61 U/L (0–60). It was noted in retrospect that on
previous blood tests taken between February and September 2021 she
had mildly elevated lipase levels between 94 and 106 U/L, however had
no history of abdominal pain to suggest pancreatitis. Alkaline phos-
phatase was 109 U/L (30–110), gamma-glutamyl transferase was 71 U/L
(0–35), alanine aminotransferase was 19 U/L (0–35) and bilirubin was
0.35 mg/dL (6 micromol/L) (<1.17 mg/dL).

In light of the risk for severe necrotizing pancreatitis, she was
admitted to hospital for urgent triglyceride lowering management. This
consisted of fasting, intravenous insulin and glucose infusions, fenof-
brate 145 mg daily and fish oil 9 g/day equating to 2700 mg omega-3.
Additionally, the rosuvastatin dose was increased from 10 mg daily to
40 mg daily. Thyroxine was also commenced at an initial dose of 25
micrograms daily to treat her mild subclinical hypothyroidism. Fasting
and the insulin/dextrose infusion continued for four days. The triglyc-
ceride level progressively fell, and she was discharged from hospital after
seven days, at which time the triglyceride concentration was 2188 mg/
dl (24.7 mmol/L) and total cholesterol was 704 mg/dL (18.2 mmol/L).
By one week after discharge, the triglycerides were down to 354 mg/dL
(4.0 mmol/L) and by 12 days after discharge, they were normal at 159
mg/dL (1.8 mmol/L) and total cholesterol was 217 mg/dL (5.6 mmol/
L). The lipase peaked at 136 U/L on Day 5 of the admission and fell to
normal by Day 8 (58 U/L).

The time course of the serum triglyceride concentration changes is
demonstrated in Fig. 1.

After reviewing the literature, paclitaxel was thought to be the likely
cause of the hypertriglyceridemia, so she was changed to a taxane-free
chemotherapy regimen of carboplatin and gemcitabine for subsequent
cycles. Following the change to gemcitabine, her triglyceride levels have
remained normal (Fig. 1). Fish oil was ceased after 6 weeks but she re-
mains on fenofibrate, and her triglyceride level was normal at 106 mg/
dl (1.2 mmol/L). It had been planned for her to have debulking surgery
around the time she developed hypertriglyceridemia; however, this was
postponed in light of the heightened perioperative risk with severe
hypertriglyceridemia. Her CA125 level had reduced to 34 U/mL in
January 2022 and follow up computed tomography demonstrated
persistent omental nodularity, with minimal decrease in volume. She
has since undergone optimal debulking surgery, and will be
commencing PARP inhibitor, Niraparib, as maintenance therapy.

3. Discussion

Platinum doublet chemotherapy is considered first line adjuvant
chemotherapy for fallopian tube serous carcinomas (Stasenko et al.,
2019). Paclitaxel in combination with cisplatin or carboplatin has been
occasionally linked with hypertriglyceridemia, however the mechanism
of this adverse event is not fully understood (Lander et al., 2020;
Watanabe et al., 2015; Wang et al., 2017 Feb 1). Lander et al described a
patient who developed severe hypertriglyceridemia (1871 mg/dL) after
the 4th cycle of intraperitoneal cisplatin and paclitaxel to treat stage IIIC
fallopian tube serous carcinoma. Intraperitoneal administration of
cisplatin and paclitaxel has an increased frequency of adverse events
compared with intravenous, including metabolic events (Armstrong
et al., 2006).

Watanabe et al reported 11 of 17 individuals in a prospective study
who received paclitaxel and carboplatin developed hyper-
triglyceridemia at 2.8 ± 0.6 courses (Watanabe et al., 2015). Triglyc-
ceride levels in these 11 individuals increased from 119 ± 23.3 to 271.5
± 108.7 mg/dL (Watanabe et al., 2015). Patients with diabetes were
excluded from that study. Wang et al reported temporally associated
hypertriglyceridemia in three women with each cycle of carboplatin and

![Fig. 1. Time course of serum triglyceride concentrations. Orange arrows represent each cycle of carboplatin/paclitaxel chemotherapy. Green arrows represent each cycle of carboplatin/gemcitabine. Red line represents normal upper limit of serum triglyceride concentration of 150 mg/dL (1.7 mmol/L).](image-url)
paclitaxel (Wang et al., 2017 Feb 1). The highest recorded triglyceride level was however <5 mmol/L (<443 mg/dL) (Wang et al., 2017).

Saito et al recently described a case of hypertriglyceridemia attributed to docetaxel, another taxane-containing chemotherapy agent, used to treat stage IIB breast cancer. The highest recorded triglyceride level was 770 mg/dL (19.9 mmol/L) in that case (Saito et al., 2021).

Dai et al have reported that paclitaxel induces aerobic glycolysis and hypertriglyceridemia (Dai et al., 2021). These metabolic effects are proposed to be linked with the excipient CrEL, which is unique to paclitaxel as compared with other taxane-containing chemotherapies. Paclitaxel, which is hydrophobic, is formulated with CrEL, which enhances drug solubility (Scripture et al., 2005). Dai et al demonstrated patients with breast cancer developed higher triglyceride levels in the group that received paclitaxel with CrEL, compared to abraxane (nanoparticle albumin-bound paclitaxel), docetaxel and non-taxanes (Dai et al., 2021). There was a triglyceride increase in all four groups, however in the paclitaxel with CrEL group, 8% developed triglyceride concentrations above 131 mg/dL (3.4 mmol/L) and 44% demonstrated a 70% rise in triglycerides after this therapy. CrEL was found to upregulate angiopoietin like 4, which is a major determinant of triglyceride levels (Aryal et al., 2019) and pre-medication with dexamethasone further accentuates this effect (Scripture et al., 2005).

The risk of acute pancreatitis increases with the concentration of serum triglyceride. The risk is approximately 5% for triglycerides >1000 mg/dL (11.3 mmol/L) and 10–20% for triglycerides >2000 mg/dL (22.6 mmol/L) (Scherer et al., 2014). Our case had serum triglyceride concentrations more than seventy times the upper limit of normal, which potentially put her at a high risk of life-threatening necrotizing pancreatitis.

This case would have escaped attention if she had not been scheduled to have routine diabetes clinic blood tests. The incidence of hypertriglyceridemia related to taxane based chemotherapy is unclear, given that lipids are not routinely assessed. At our institution, routine full blood count, renal function test and liver function test are monitored prior to each cycle of chemotherapy, in addition to hepatitis B serology screening prior to commencement. Lipid levels are not part of our standard practice for monitoring.

Our patient had several factors which may have pre-disposed her to massive hypertriglyceridemia: a history of dyslipidemia, type 2 diabetes, post-menopausal status, glucocorticoid therapy, and subclinical hypothyroidism. While these factors may have predisposed her to hypertriglyceridemia, the use of paclitaxel was clearly temporally linked, and in addition, hypertriglyceridemia has not recurred when using alternative chemotherapy agents. All of this suggests the paclitaxel was responsible. It is possible that she has a genetic defect pre-disposing her to this reaction. Genetic studies have not been performed.

We suggest it is important to assess lipid panels prior to and serially in patient receiving taxane chemotherapy. This is especially relevant to patients with a history of type 2 diabetes or dyslipidemia.

In summary, we report a case of severe hypertriglyceridemia attributed to paclitaxel use. To our knowledge this is the most severe triglyceride elevation reported related to paclitaxel. Treating oncologists should be aware of this potential effect and monitoring of lipid panels should be considered in individuals receiving this chemotherapy regimen, especially in people with type 2 diabetes or a history of dyslipidemia. This would minimise harmful potential sequelae of hypertriglyceridemia and enable prompt commencement of triglyceride lowering therapy and/or alteration of administered chemotherapy.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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CRediT authorship contribution statement

Anojan Koneshamoorthy: Writing – original draft, Investigation, Visualization. Danielle Hulse: Investigation, Visualization. Chia Yuen Chong: Writing – review & editing. Balasubramanian Krishnamurthy: Writing – review & editing. Sumitra Ananda: Writing – review & editing. Peter S. Hamblin: Investigation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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