CASE REPORT

Tamoxifen precipitation of familial hypertriglyceridaemia: a rare cause of acute pancreatitis

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SUMMARY

Drug-induced pancreatitis is uncommon, and is estimated to account for between 0.1% and 5% of cases. Tamoxifen is commonly used in the management of oestrogen receptor-positive breast cancer. We present a rare case of tamoxifen-related hyperlipidaemia resulting in repeated episodes of pancreatitis, which, to the best of our knowledge, has only been documented a few times in the literature. A 36-year-old woman with familial hypertriglyceridaemia presented with recurrent episodes of abdominal pain, modest increases in serum amylase levels and normal liver function tests. The patient had recently been diagnosed with breast carcinoma and was managed with wide local excision (WLE), adjuvant radiotherapy and tamoxifen. On each admission, the patient's symptoms were confirmed either biochemically and/or radiologically. Analysis of the case led to a diagnosis of precipitation of familial hypertriglyceridaemia from tamoxifen use resulting in pancreatitis. Management was altered with tamoxifen cessation and initiation of second-line hormonal therapy. Tamoxifen use needs consideration, especially in those with familial hyperlipidaemia.

BACKGROUND

This case demonstrates the importance of accurate history taking and particularly that of a drug history.^{1 2} This is of even more importance in patients with recurrent presentations to hospital, especially when common causes for the patient's symptoms have been excluded. Marked hypertriglyceridaemia can produce acute pancreatitis. Furthermore, only a handful of similar case reports have been documented worldwide and, to the best of our knowledge, none have been reported in the UK.

CASE PRESENTATION

A 36-year-old Asian woman was started on tamoxifen as an adjuvant treatment of oestrogen receptor-positive grade 1 invasive tubular carcinoma. Two months following the initiation of tamoxifen, the patient presented to our unit with a several day history of upper abdominal pain, nausea and vomiting. Her medical history included familial hypertriglyceridaemia with pre tamoxifen lipid levels; triglycerides 8.5 mmol/L (normal range <2.3 mmol/L) (figure 1), cholesterol 4.3 mmol/L (normal range 2.5–5 mmol/L), high density lipoprotein (HDL) 0.7 mmol/L (normal range >1.2 mmol/L). The patient was known to have

gallstones confirmed on a previous ultrasound scan. She was a non-smoker and denied alcohol use. There was no recent history of foreign travel. Serum amylase level was only slightly elevated and all liver function tests were within the normal range. Table 1 below shows the amylase level and results of liver function tests. A CT scan of the abdomen and pelvis showed resolving pancreatitis. The patient settled with conservative management. Following discharge, she underwent an uneventful laparoscopic cholecystectomy in the following few weeks.

Over the following 3 months, the patient had a further two admissions with abdominal pain, and again with mild increases in serum amylase. Table 1 below shows the amylase level and results of liver function tests. In combination, clinical and radiological features suggested resolving presentations of pancreatitis. Given her medical history of familial hypertriglyceridaemia, a lipid profile was performed which revealed elevated levels of triglycerides; 55 mmol/L, cholesterol 14.1 mmol/L and HDL 0.4 mmol/L. A diagnosis of pancreatitis secondary to hyperlipidaemia was made and the patient was referred to metabolic medicine. She was started on fenofibrate (160 mg once daily) in an attempt to prevent future attacks.

The patient was followed up by the metabolic medicine team resulting in her fenofibrate dose increasing to 267 mg once daily and subsequent introduction of omacor prescribed as two capsules to be taken once daily. Triglyceride levels returned to 7.5 mmol/L following the increase in dose of fenofibrate to 267 mg once daily.

Despite antilipid treatment, the patient had a fourth episode of CT-confirmed pancreatitis, with slightly raised amylase once again. Table 1 below shows the amylase level and results of liver function tests. She was discharged home when clinically better but returned for a fifth time 5 days following discharge in October 2015 with symptoms of upper abdominal pain and vomiting. Table 1 below shows the amylase level and results of liver function tests. A lipid profile was again performed and was once again markedly deranged; triglycerides levels had again risen to 26.8 mmol/L, cholesterol 7.1 mmol/L and HDL 0.4 mmol/L. Atorvastatin 10 mg once daily was added and dietary modifications were reinforced. Although liver function tests were normal, an magnetic resonance cholangiopancreatography (MRCP) was performed and excluded residual ductal stones.

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Figure 1 Graph demonstrating episodes of acute pancreatitis in relation to triglyceride levels and highlighting treatment administered following each episode of acute pancreatitis. The significance of the * in red are to signify when each episode of acute pancreatitis occurred in relation to the triglyceride level at different time points and the treatment patient received over the course of time. OD, once daily.

Given the repeated episodes of pancreatitis in a patient with no other cause to precipitate these episodes, tamoxifen was thought to be the cause for precipitation of hypertriglyceridaemia causing pancreatitis. Following a breast multidisciplinary team meeting, a decision was made to stop tamoxifen. The patient was started on goserelin and anastrozole. Until now, the patient has been well and she has had no further admissions to hospital. The most recent triglyceride level was 5 mmol/L, HDL 0.5 mmol/L and cholesterol 2.8 mmol/L.

DISCUSSION

Acute pancreatitis is a serious condition with potentially life-threatening complications. Common causes, particularly in the Western world, include excessive alcohol consumption and gallstones. Although rare, hypertriglyceridaemia is thought to be the third most common cause accounting for 7% of cases.³ Numerous other causes resulting in pancreatitis include trauma, viral illnesses, electrolyte abnormalities, iatrogenic injuries (eg, post endoscopic retrograde cholangiopancreatography) and certain medications. This latter group, as previously mentioned, may account for up to 5% of cases.²

The aetiology of drug-induced pancreatitis has been put-down to a number of different mechanisms including an accumulation of toxic metabolites triggering pancreatic inflammation, hypersensitivity reactions in susceptible individuals or, as in this case, through effects on lipid metabolism.⁴

Tamoxifen is an antioestrogenic agent and it is for these properties that it has now become a well-established treatment for patients with breast cancer. Tamoxifen paradoxically displays oestrogenic effects on lipid metabolism.² It is thought to stimulate the endogenous production of triglycerides leading to hypertriglyceridaemia, overloading serum clearance of this substance by enzymes such as lipoprotein lipase.⁵ These enzymes become saturated and a substantial build-up of triglycerides occurs, a situation similar to rare inherited disorders of lipid metabolism.

For hypertriglyceridaemia to cause pancreatitis, it has been reported that the triglyceride levels are usually in excess of 20 mmol/L.⁶ These levels are usually associated with individuals who have a primary or genetic disorder of lipid metabolism. This is then aggravated by a secondary cause.

In the acute setting, the management of pancreatitis remains the same and consists mainly of supportive therapy. In terms of developing further complications, pancreatic necrosis and other outcomes, hyperlipidaemia-induced pancreatitis is similar to other causes of pancreatitis.⁶

A number of other strategies to treat pancreatitis have been documented in the literature.⁶ They include measures such as chronic plasmapheresis as a prophylaxis to prevent repeated attacks of hyperlipidaemia-induced pancreatitis. Longer term management of these cases is twofold and often involves input from other specialties. The identification and cessation of drugs that may cause pancreatitis is important in addition to therapies directed at lowering lipid levels. Stopping important drugs such as tamoxifen should always be discussed with the specialist team. Lifestyle advice, cessation of alcohol, dietary modifications and exercise are all necessary and important in the management of these patients.

Lipid-lowering agents also have a role and need to be considered. Fibrates are usually first choice and are generally well tolerated. Additional adjuncts in refractory cases may be added such as omega-3 fatty acid products.⁶

While the patient had a family history of familial hypertriglyceridaemia and was initially diagnosed with acute pancreatitis secondary to hyperlipidaemia, despite antilipid treatment an initial reduction in triglyceride levels was short-lived and was again followed by a rise in triglyceride levels which was noted when the patient presented on her fifth admission. While it would be difficult to attribute acute pancreatitis solely to tamoxifen intake, it is much more likely that the patient's familial

Table 1 Demonstrating liver function tests, serum amylase level +/- lipid profile on each admission with acute pancreatitis

Episode of pancreatitis	Liver function tests				Serum amylase level (U/L)	Lipid profile	CT performed
First	ALT <30 (U/L)	ALP 80 (U/L)	Albumin 39 (g/dL)	Bili 14 (μmol/L)	139	Not performed	Yes
Second	ALT <30	ALP 74	Albumin 39	Bili 3	80	Not performed	Yes
Third	ALT <30,	ALP 60	Albumin 37	Bili 7	157	Triglycerides 55 mmol/L, cholesterol 14.1 mmol/L and HDL 0.4 mmol/L	Yes
Fourth	ALT <30	ALP 83	Albumin 38	Bili-Bilirubin analysis unsuccessful due to a lipaemic sample	77	Not performed	Yes
Fifth	ALT <30	ALP 56	Albumin 37	Bili 10	367	Triglycerides 26.8 mmol/L, cholesterol 7.1 mmol/L and HDL 0.4 mmol/L	No

ALP, alkaline phosphatase; ALT, alanine transaminase.

ALT- units per liter (U/L); ALP- units per liter (U/L); ALBUMIN- grams per deciliter (g/dL); BILIRUBIN- μmol/L; Amylase- units per liter (U/L).

hypertriglyceridaemia was precipitated by tamoxifen intake. This is very likely given that the patient had not experienced pancreatitis previously prior to the initiation of tamoxifen therapy and furthermore as the triglyceride level recorded prior to tamoxifen initiation was 8.5 mmol/L.

Detecting an adverse drug reaction is not always an easy task as has been demonstrated here. Following the fifth attack, tamoxifen was identified as causing an adverse reaction and was subsequently stopped with a successful outcome. Review of medications and recognising a known side effect of tamoxifen (precipitating triglyceride levels) was key. One of the difficulties in identifying adverse drug reactions is that the onset of an adverse reaction can occur sometime after the initiation of the drug. Following a literature review search, 'tamoxifen-induced pancreatitis', yielded 423 search results on Pubmed. Only eight case reports were found to exist worldwide. *Lin et al*⁷ in 2004 reported a case of tamoxifen-induced pancreatitis with onset of pancreatitis reported 24 months after initiation of tamoxifen. Furthermore, *Artac et al*⁸

in 2002 reported a case of tamoxifen-induced pancreatitis 18 months after the initiation of tamoxifen.

This case represents a rare but interesting manifestation of a common medical problem. It is hoped that from the case and the subsequent discussion it has been noted that marked hypertriglyceridaemia can produce acute pancreatitis. A comprehensive history and clinical examination needs to be performed with a particular emphasis on a meticulous medical history and current medications. Initial treatment of acute pancreatitis remains supportive. Longer term nutritional and pharmacological therapy together with the cessation of potential precipitants can be successful in the prevention of further episodes in such patients.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- ▶ Accurate drug history is vital.
- ▶ Marked hypertriglyceridaemia can produce acute pancreatitis.
- ▶ Regular monitoring of lipid profiles may be required for patients taking tamoxifen.
- ▶ Tamoxifen may require cautious use in those patients with a familial predisposition of hyperlipidaemia.
- ▶ Alternative hormonal treatments for patients being managed for breast cancer with a medical history including familial hypertriglyceridaemia.

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