

Tamoxifen-induced acute pancreatitis – a case report

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Abstract

Tamoxifen is a selective estrogen receptor modulator used for the treatment of oestrogen/progesterone receptor positive breast cancer. It has antagonistic or agonistic activity depending on the tissue location. Generally it causes mild and reversible side effects, however more serious ones including cardiovascular and thromboembolic adverse events, uterine cancer or acute pancreatitis can also occur. Tamoxifen, like oestrogens, increases the plasma level of TG and liver secretion of VLDL. Moreover, it inhibits the key enzymes of triglyceride metabolism. In this report we present a case of a 55-year-old woman with a history of a poorly controlled hypertriglyceridaemia diagnosed with breast cancer. She was treated with surgery and adjuvant chemotherapy, radiotherapy and hormone therapy with tamoxifen. About three months after hormonal treatment, her triglyceride level increased. Five months later she developed an acute necrotic pancreatitis that required hospitalization. Her serum samples on admission were highly lipemic. An abdominal ultrasound showed no evidence of gallstones or dilation of the bile ducts. There was no history of alcohol abuse or abdominal trauma. Tamoxifen was suspected as a trigger factor for pancreatitis. After the drug withdrawal and administration of the conservative management the patient's medical condition improved. Due to a postmenopausal status of the patient and no harmful effect on serum lipids, an adjuvant hormone therapy with aromatase inhibitor was started.

Key words: tamoxifen, pancreatitis, hypertriglyceridaemia.

Introduction

Tamoxifen is a selective estrogen receptor modulator (SERM) with ability to prevent the binding of endogenous oestrogens to oestrogen receptor on cancer cells. It is used in the treatment of breast cancer patients (in preoperative, adjuvant, and palliative therapy). Tamoxifen is one of the best known and best tolerated anticancer drugs. As oestrogen receptors are present on many non-cancer cells and in some normal tissues, tamoxifen has bifunctional, i.e. antagonistic and agonistic, activity, the effect of this drug is not selective and can lead to some, generally rare and mild, side effects. The most common and reversible ones are hot flashes, fluid retention, nausea, vomiting, vaginal bleeding or discharge. However, very rare serious adverse events like cardiovascular and thromboembolic events or uterine cancer could be sometimes life-threatening. Tamoxifen may also alter serum lipid levels, thereby contributing to the increase in the risk of acute pancreatitis.

Case report

A 55-year-old postmenopausal woman with a history of dyslipidemia and acute pancreatitis with mild symp-

toms (in 2010) was diagnosed with ductal breast cancer in January 2012. She had breast-conserving treatment of the right breast with sentinel lymph node biopsy, and – because of the lymph node involvement – a total axillary lymph node dissection afterwards. The pathological staging was: pT2pN1a (tumour diameter of 25 mm, 3 of 42 metastatic lymph nodes), grade 2. The tumour expressed both oestrogen (100% cells/3, TS 8/8) and progesterone receptor (100% cells/3, TS 8/8). There was no overexpression of HER-2 (1+). From April 2012 to September 2012, the patient received a sequential adjuvant chemotherapy with 4 cycles of AC regimen (doxorubicin 60 mg/m², cyclophosphamide 600 mg/m² every 3 weeks) followed by 4 cycles of docetaxel (100 mg/m² every 3 weeks). There were no clinically significant side effects during chemotherapy. Three weeks after the last dose of docetaxel she started adjuvant hormone therapy with tamoxifen (20 mg daily). From October to November 2012, she received adjuvant radiotherapy (conformal 3D) on the field of the right breast and supraclavicular lymph nodes (photons of 6 MV and 15 MV to a total dose of 50 Gy) with boost to the site of excision (electrons of 12 MeV to 60 Gy). In May 2013, she started to feel discomfort with her stomach – she had dyspeptic symptoms and flatulence. The woman also

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noticed swelling of her legs and an abdominal distention. There were no other suspicious symptoms. In June 2013, the patient was admitted to the local hospital due to acute strong girdle pain of stomach. Her serum samples on admission were so lipemic (milk-like) that made blood testing impossible. In urine, there was an increased activity of amylase reaching 552 U/l. Two days after admission the serum was still highly lipemic, however laboratory tests showed the following values: white blood cell count (WBC) 9.46×10^3 with 31% of immature neutrophils (30% band forms and 1% metamyelocytes), haemoglobin (Hgb) 13.5 g/dl, hematocrit (Hct) 33.2%, hypernatremia 147 mmol/l, hypokalemia 2.21 mmol/l, hypocalcemia 1.87 mmol/l, high CRP (C-reactive protein) 286.49 mg/l; amylase activity in urine reached 3222 U/l. Fasting glycemia was 104 mg/dl. Several days later, assayed activity of serum amylase was 32 U/l (within normal range) and activity of serum lipase was 75 U/l (elevated). Blood urea nitrogen, creatinine, bilirubin, total protein were within normal limits. Triglycerides (TG) level was not evaluated. An abdominal ultrasound showed no evidence of gallstones or dilation of the bile ducts, however bowels were filled up with fluid and peristalsis was slow; moreover the patient's liver was hyperechogenic. Computed tomography revealed: fragmented body and tail of pancreas; irregular communicating fluid collections in the peripancreatic region and in epigastrium; on the left side of abdomen there was also a fluid collection with septums and insertions $58 \times 89 \times 187$ in dimension with downward extension to the left iliac fossa; there was also a fluid in pelvis and in right pleura. The patient was diagnosed with acute necrotic pancreatitis. Conservative management was initiated with antibiotics, FFP (fresh frozen plasma) transfusions, albumin and crystalloids infusions, electrolytes and painkillers. Haemoglobin level decreased during hospitalization to 7.0 g/dl so the patient required PRBCs (packed red blood cells) transfusions. Because of no history of alcohol abusing or abdominal trauma, tamoxifen was suspected as a possible trigger of pancreatitis and the drug was immediately withdrawn. The patient got better after three weeks of hospitalization. She had a control blood test seven weeks after being discharged from hospital. Cholesterol level without lipid-lowering therapy was 143 mg/dl, HDL was 29 mg/dl, LDL 41 mg/dl, and TG were 365 mg/dl. Adjuvant hormone therapy was continued with a change from tamoxifen to anastrozole (1 mg daily) with good tolerance.

Discussion

Acute pancreatitis caused by drugs is an unusual entity. The diagnosis is hard to determine because of its rarity and no precise criteria to distinguish medicament-related aetiology from other causes (e.g. alcohol use, biliary tract disease or gallstones, abdominal trauma,

hypercalcemia). The pathogenesis of drug-induced pancreatic injury is not clear. Some classifications include intrinsic toxicity which is rare (e.g. erythromycin, carbamazepine) or idiosyncratic reactions. In the intrinsic toxicity mechanism drugs cause organ damage in a dose-dependent manner, reproducibly and do not correlate with host response. Conversely, idiosyncratic reactions do not depend on the drug dose and their occurrence cannot be predicted. They involve hypersensitivity reactions that are accompanied by classic symptoms of hypersensitivity (i.e. azathioprine/6-merkaptopurine, captopril), accumulation of toxic metabolite (i.e. valproic acid, 2'3' dideoxyinosine) or intermediary injurious substance (i.e. tamoxifen, oestrogens) [1]. In a case of tamoxifen or oestrogen-induced pancreatitis, hypertriglyceridaemia (a well-known risk factor for acute pancreatitis) is a possible intermediary leading to the event. However, the mechanism by which elevated triglycerides induce pancreatic injury is unclear. One theory relates it to an impaired clearance of chylomicrons that can obstruct capillaries and lead to pancreatic ischemia. Another theory suggests that pancreatic lipase hydrolyses an excess of TG to free fatty acids that induce inflammatory changes [2].

As far as oestrogens are concerned in pathogenesis, acute pancreatitis is typically associated with TG level of more than 1000 mg/dl and recurrent pancreatic injury occurs within several months after treatment challenge [3]. It is also important to know that the serum amylase level can be normal in a setting of hypertriglyceridaemia which may confuse the diagnosis.

Pharmacological activity of tamoxifen on oestrogen receptor is bifunctional – antagonistic and agonistic. Its influence on lipid metabolism is determined by agonistic effect [4]. Tamoxifen, like oestrogens, increases the plasma level of TG and liver secretion of VLDL (very low density lipoproteins) – the main carrier of TG. Moreover, tamoxifen administration decreases the activity of LPL (lipoprotein lipase) and hepatic triglyceride lipase (HTGL). Therefore, it inhibits the key enzymes of triglyceride metabolism [5]. Data from published trials reveal that there is only a modest increase in serum TG levels, however sometimes treatment may cause a severe increase in TG [5, 6]. It is more probable to induce very high TG levels in patients with a history of dyslipidaemia, nevertheless it is not a rule [7, 8]. In Pubmed database (access on 30 October 2013) only seven case reports of tamoxifen-induced pancreatitis have been published.

The described patient had a history of previous hypertriglyceridaemia, probably genetically determined. She was first diagnosed with an elevated TG level at the age of 38, her mother was also diagnosed with some not-specified lipidemic disorder. She used fenofibrate but several self-decided episodes of drug withdrawal and non-adherence to diet occurred. The high-

Table I. The influence of hormonal therapy of breast cancer on lipids levels [4]

Hormonal therapy	TC	LDL	HDL	TG	TC/HDL-C	LDL-C/HDL-C
tamoxifen	↓	↓	↑ or ↓ or n.c.	↑	n.c.	↓
anastrozole	↓ or ↑ or n.c.	↓ or ↑ or n.c.	↑	↓	n.c.	n.c.
letrozole	↑ or n.c.	↑ or n.c.	–	–	↑	↑
exemestane	n.c. or ↓	n.c. or ↓	↑ or ↓ or n.c.	↓	n.c.	–

TC – total cholesterol, LDL-C – low density lipoprotein cholesterol, HDL-C – high density lipoprotein cholesterol, TG – triglyceride, ↑ – increase, ↓ – decrease, n.c. – no change, “–” – no data

est level of TG reached 940 mg/dl in 2004. The patient's first episode of acute pancreatitis with mild symptoms was diagnosed in 2010. Since that episode the dose of fenofibrate has been increased. However, the patient still frequently discontinued taking the lipid-lowering drug for some short periods. Her TG level in December 2011 (before any anti-cancer therapy started) reached 332.3 mg/dl, however in November 2013 (3rd month of tamoxifen treatment) it increased to 664 mg/dl. Severe acute pancreatitis occurred eight months after tamoxifen commencement during therapy with fenofibrate (215 mg daily). As summarized in the literature, in most cases the onset of severe pancreatitis is less than one year since tamoxifen induction [1, 7]. The relationship of the first severe episode of pancreatitis with tamoxifen administration and an improvement after drug withdrawal led us to suspect tamoxifen as a possible trigger agent. Due to the postmenopausal status of the patient and no harmful effect on serum lipids (Table I), an adjuvant hormone therapy with aromatase inhibitor anastrozole was started and this drug was well tolerated. More than three months after the episode of pancreatitis (and withdrawal of tamoxifen) during treatment with fenofibrate, TG concentration reached 130 mg/dl.

As tamoxifen therapy could alter lipid metabolism and induce severe pancreatitis, clinicians should consider possible benefits of its administration and the risk of side effects especially in patients with a history of dyslipidemia. Moreover, in that case it is important to monitor plasma lipids periodically, especially in patients with co-existing significant lipid disorders. When hypertriglyceridaemia is diagnosed, appropriate diet

and antilipemic drugs ought to be recommended because these two complementary methods are effective in reducing the risk of hypertriglyceridaemia-induced pancreatitis [9]. However, in a case of severe acute pancreatitis with tamoxifen as a probable causative agent the drug should be discontinued and an alternative treatment should be started.

Disclosure

Authors report no conflicts of interest.

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