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 hormonotherapy 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 hormonotherapy with aromatase inhibitor was started.

Key words: tamoxifen, pancreatitis, hypertriglyceridaemia.
Fasting glycemia was 104 mg/dl. Several days later, amylase activity in urine reached 3222 U/l. hypocalcemia 1.87 mmol/l, high CRP (C-reactive protein) hypernatremia 147 mmol/l, hypokalemia 2.21 mmol/l, haemoglobin (Hgb) 13.5 g/dl, hematocrit (Hct) 33.2%, neutrophils (30% band forms and 1% metamyelocytes), (1 mg daily) with good tolerance. continued with a change from tamoxifen to anastrozole 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 hypercho- genic. Computed tomography revealed: fragmented body and tail of pancreas; irregular communicating fluid collections in the peripancreatic region and in epigas- trium; on the left side of abdomen there was also a fluid collection with septums and insertions 58 × 89 × 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 pancreaticitis. 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 ther- apy was 143 mg/dl, HDL was 29 mg/dl, LDL 41 mg/dl, and TG were 365 mg/dl. Adjuvant hormonotherapy 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 medication-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-merkapto purine, 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 rechallenge [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 li- pase (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 feno- fibrate but several self-decided episodes of drug withdrawal and non-adherence to diet occurred. The high-
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.

References

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

<table>
<thead>
<tr>
<th>Hormonal therapy</th>
<th>TC</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
<th>TC/HDL-C</th>
<th>LDL-C/HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>tamoxifen</td>
<td>↓</td>
<td>↓</td>
<td>↑ or ↓ or n.c.</td>
<td>↑</td>
<td>n.c.</td>
<td>↓</td>
</tr>
<tr>
<td>anastrozole</td>
<td>↓ or ↑ or n.c.</td>
<td>↓ or ↑ or n.c.</td>
<td>↑</td>
<td>↓</td>
<td>n.c.</td>
<td>n.c.</td>
</tr>
<tr>
<td>letrozole</td>
<td>↑ or n.c.</td>
<td>↑ or n.c.</td>
<td>–</td>
<td>–</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>exemestane</td>
<td>n.c. or ↓</td>
<td>n.c. or ↓</td>
<td>↑ or ↓ or n.c.</td>
<td>↓</td>
<td>n.c.</td>
<td>–</td>
</tr>
</tbody>
</table>

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

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.

References