Acute pancreatitis following clomiphene citrate treatment: Case report and review of the literature

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Clomiphene citrate is a synthetic estrogen analog, which exerts some estrogenic, but predominantly anti-estrogenic effects. Although it has been widely used for more than 40 years for the treatment of anovulatory infertility, not much is known about its influence on lipid metabolism. Similar to estrogen and tamoxifen, it probably increases the level of triglycerides in patients with baseline hypertriglyceridemia.1 Severe hypertriglyceridemia might lead to a potentially lethal complication such as acute pancreatitis. Therefore, awareness of this condition is of utmost importance. Herein we present such a case, followed by a review of the literature.

Patient description

A 27-year-old woman was admitted with diffuse abdominal pain, fever, nausea, and vomiting of one day duration. Positive findings on physical examination included obesity, hirsutism, and a diffusely tender abdomen without peritoneal signs. Abnormal laboratory tests consisted of lipase 550 (normal < 60 U/L), triglycerides 1845 (normal < 150 mg/dl) and WBC 18,400 (normal < 11,000 K/mcl). She was diagnosed as suffering from acute pancreatitis, most probably due to hyperlipidemia, since abdominal sonography revealed an acalculous gallbladder, and alcoholism was denied per anamnesis.

Past medical history included gout treated by allopurinol and colchicine, mild hypertriglyceridemia (past values of 316 and 450 mg/dl) treated occasionally by a fibrate (SR; Hennig, Medison Pharma), and diabetes mellitus type II treated by a low glucose diet. As a result of failure to conceive, clomiphene citrate was prescribed about 6 months prior to her admission. The dose was increased gradually from 50 mg to 150 mg for 5 consecutive days a week ending 15 days prior to her admission.

She was discharged after 5 days with instructions not to use similar infertility drugs thereafter and to resume treatment with a fibrate and a low-fat diet.
Five months later, she was rehospitalized due to recurrent pancreatitis. Anamnesis revealed non-compliance with the fibrate treatment and resumption of the clomiphene citrate treatment, ending 10 days prior to admission. A triglyceride level of 6800 mg/dl was recorded and treatment with a fibrate was reinitiated. She was discharged 4 days later and had no recurrences during an 8-month follow-up period.

Comment

Hyperlipidemia constitutes one of the major causes of acute pancreatitis. The mechanism probably involves the release of large amounts of toxic fatty acids by pancreatic lipase that damages the endothelium in the capillaries of the pancreas. This results in sludging of red blood cells, stasis, pancreatic ischemic injury and eventually inflammation. In addition, physical damage by cholesterol crystals might cause microvascular endothelial cell disruption.

It has been reported that severe drug-induced triglyceride levels >1000 mg/dl are more common in patients with underlying familial hypertriglyceridemia. Exogenous factors which raise triglyceride levels include exogenous estrogens, corticosteroids, beta-blockers, diuretics, selective estrogen receptor modulators, clomiphene, isotretinoin, protease inhibitors, hyperestrogenemia of pregnancy, poorly controlled diabetes mellitus, hypothyroidism, multiple myeloma, systemic lupus erythematosus, lymphoma and alcohol excess.

Exogenous estrogens elevate triglycerides by increasing the production of triglyceride-carrying very low density lipoproteins (VLDLs) by the liver and reducing the levels of lipoprotein lipase (LPL) and hepatic lipase, thus reducing triglyceride clearance, while also elevating triglycerides by augmentation of insulin resistance.

Tamoxifen is known to cause a small, but significant decrease in high-density lipoprotein (HDL) cholesterol, unlike estrogen, which elevates HDL. In women with hypertriglyceridemia, tamoxifen’s ability to increase the triglyceride level is especially pronounced, to an extent that may induce acute pancreatitis.

Clomiphene citrate is a synthetic estrogen analog with a biochemical structure similar to that of tamoxifen. Clomiphene has mixed agonistic, but mainly antagonistic properties.

We presume that the effects of clomiphene on lipid metabolism have not been as well-documented as the effects of tamoxifen because it is not used continuously and not as commonly as tamoxifen. Clomiphene elevates the triglyceride level mainly in women with a predisposed risk for hypertriglyceridemia, due to mutations in enzymes such as LPL.

To the best of our knowledge, this is the second report on clomiphene citrate-induced hypertriglyceridemic acute pancreatitis.

In conclusion, clomiphene citrate is one of the most common drugs used to treat infertility. Given the structural similarity between clomiphene citrate and tamoxifen, it is likely that it is capable of causing severe hypertriglyceridemia in a manner similar to that of tamoxifen, which can eventually induce pancreatitis.

We suggest that prior to commencing treatment with clomiphene citrate, the triglyceride level should be measured, in order to avoid hypertriglyceridemic acute pancreatitis and exacerbation of overt or covert familial hypertriglyceridemia. In women with preexisting hypertriglyceridemia (triglycerides ≥500 mg/dl), clomiphene citrate should be avoided.

References