

## Acute Pancreatitis Secondary to the Drug Tamoxifen: About a New Clinical Case

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### Abstract

### Case Report

Drug-induced acute pancreatitis is a rare pathology with a pathophysiology that is poorly understood. The diagnosis is made after eliminating the other classic causes of pancreatitis. The treatment behind the acute pancreatitis should be stopped permanently. We report a new observation of a case with acute drug-induced pancreatitis after a prolonged use of tamoxifen.

**Keywords:** Drug-induced acute pancreatitis - Hypertriglyceridemia - Tamoxifen.

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## INTRODUCTION

Acute drug-induced pancreatitis is a rare condition [1, 2], defined by the occurrence of a flare-up of pancreatitis after the administration of a drug while eliminating other classic causes [3]. Several drugs have been implicated in the occurrence of drug-induced pancreatitis, cases of acute pancreatitis have been reported under treatment with tamoxifen, which acts by inhibiting the growth of tumor cells by competitive estrogen antagonism. It was developed for the treatment of breast cancer in the 1970s. It was the first antiestrogen available and, for almost 30 years, the gold standard until the arrival of aromatase inhibitors for postmenopausal patients [1].

We report a new case of hypertriglyceridemia and acute drug-induced pancreatitis following prolonged use of tamoxifen.

## CASE REPORT

We report the clinical case of a 42-year-old patient who was treated for a cancer of the left breast for 6 years, for which she underwent a left mastectomy followed by concomitant radio chemotherapy and then treated with tamoxifen at a dose of 20 mg/d, the exposure time was 9 months. The patient was admitted to our department for epigastralgia with dorsal irradiation occurring after a copious dinner, associated with bilious vomiting. The history showed no evidence of known dyslipidemia or alcohol consumption. The clinical examination objectified an apyretic patient,

stable on the hemodynamic and respiratory conditions with an epigastric tenderness. The blood tests noted a lipasemia level at 2907 IU / L ( $> 3N$ ), thus the diagnosis of acute pancreatitis was concluded. Regarding the rest of the biological assessment, hypertriglyceridemia was objectified at 950 mg dl while the blood count, blood ionogram, calcium level and hepatic tests were normal. As part of the assessment of this case, there were no signs of clinical or laboratory severity according to the SIRS score, and abdominal CT had found acute stage C Balthazar pancreatitis (Image-1). The gallbladder was alithiasis and the intra and extra hepatic bile ducts were not dilated. The drug origin was then suspected justifying the interruption of treatment.

The management of acute pancreatitis was based on resting the digestive tract, rehydration, analgesics, anti-ulcer prevention by a proton pump inhibitor, with a good clinical and biological evolution. Other tests were made to eliminate the other causes of acute pancreatitis such as an auto-immune test was requested, in particular for the dosage of IGG4 which returned negative, the diagnosis of acute pancreatitis secondary to tamoxifen was then retained. The evolution was marked by a marked clinical improvement (disappearance of pain), and biological improvement (normalization of lipasemia and triglyceridemia) after stopping the treatment in question, a diet and lipid-lowering treatment. After that, the patient was referred to his attending oncologist to discuss changing the treatment.



Image-1: Acute stage C Balthazar pancreatitis

## DISCUSSION

Acute drug-induced pancreatitis is a rare condition. Its prevalence varies from 1 to 2% depending on the study [4, 5]. It is defined by the occurrence of an outbreak of pancreatitis after the introduction of a drug or after an increase in its doses, and this in the absence of a classic cause of pancreatitis [6]. On the semiological level, there is no difference between acute drug-induced pancreatitis and another [7].

In the most cases, acute drug-induced pancreatitis is presented as an edematous type with a limited progression over time if the suspected drug was suspended [8]. However, in 10 to 15% of cases, there is an evolution towards severe necrosis of the pancreas with high mortality [7, 9].

Several pathophysiological mechanisms leading to drug-induced pancreatitis have been suggested, including: a hypersensitivity reaction that occurs within four to eight weeks of starting treatment, an accumulation of toxic metabolite that causes pancreatic damage occurring months after the start of treatment, in particular in the case of drugs inducing hypertriglyceridemia (Thiazides, Tamoxifen, Isotretinoin) or even intrinsic activity inducing pancreatic lesions in the case of overdose [2, 10].

Tamoxifen exhibits antagonist and agonist activity at estrogen receptors. Its influence on lipid metabolism is determined by its agonist effect [11, 12]. It stimulates the synthesis and hepatic secretion of very low density lipoproteins (VLDL), which is the main transporter of triglycerides, and which decreases the catabolism of Intermediate Density Lipoproteins (IDL) and Very Low Density Lipoproteins (VLDL), by decreased activity of hepatic lipoprotein lipase and triglyceride lipase, which are key enzymes in the catabolism of triglycerides, and resulting in increased Triglycerides [13, 14].

The main possible mechanism leading to acute tamoxifen-induced pancreatitis is hypertriglyceridemia, with a triglyceride (TG) level higher than 1000 mg / dl [15]. However, the pathophysiology of pancreatic lesions is not yet clear. Few theories that have been postulated to explain this phenomenon [16], in particular an altered clearance of chylomicrons leading to obstruction of the capillaries, which causes pancreatic ischemia, or pancreatic lipase which hydrolyses excess triglycerides into free fatty acids causing inflammatory changes.

As far as we know, very few cases of acute pancreatitis induced by tamoxifen have been reported in the literature (Table-1). The dose of tamoxifen was 20 mg / day, except in one patient, whose dose was 10 mg / day. In most cases there was a history of dyslipidemia, however our patient did not have any history of previous dyslipidemia. This suggests that regular blood tests of lipid status are needed in all patients on tamoxifen.

The serum triglyceride level that caused the acute pancreatitis ranged from 900 to 7000 mg / dl. The episode of acute pancreatitis has occurred in the majority of reported cases within 6 months of starting treatment with tamoxifen. The severity also varied in the reported cases, the majority had mild pancreatitis with a favorable evolution like our patient's case, while only one patient had necrotizing pancreatitis.

Table-1

Author	Age (years)	History of dyslipidemia	Dosage mg/day	Triglyceridemia (mg/dl)	Time onset (months)	Evolution
Noguchi M <i>et al.</i> , 1987 [17]	34	Not specified	20	3673	7	Death
Colls BM, George PM <i>et al.</i> , 1998 [18]	44	Yes	Not Specified	6984	Not specified	Favorable
Elisaf MS <i>et al.</i> , 2000 [19]	53	Yes	20	5200	8	Favorable
Artac M <i>et al.</i> , 2002 [3]	51	Not specified	10	1344	12	Favorable
Lin HH <i>et al.</i> , 2004 [19]	43	Yes	Not specified	1040	24	Favorable
Alagozlu H <i>et al.</i> , 2006 [21]	46	Yes	20	900	12	Favorable
Sakhri J <i>et al.</i> , 2010 [22]	44	No	20	1180	12	Favorable
Czyzykowski R <i>et al.</i> , 2014 [23]	55	Yes	20	Not specified	9	Favorable
Kim <i>et al.</i> , 2014 [24]	40	No	20	3241	3	Favorable
Kataria <i>et al.</i> , 2017 [2]	50	No	20	1050	1	Favorable
Tey <i>et al.</i> , 2019 [25]	55	No	20	3883	24	Favorable
Our case (2020)	42	No	20	<b>950</b>	9	Favorable

Treatment with tamoxifen may alter lipid metabolism, and induce severe pancreatitis, clinicians should consider the possible benefits of its administration and the risk of side effects, especially in patients with a history of dyslipidemia. When hypertriglyceridemia is detected, an appropriate diet and lipid-lowering drug therapy are suggested to reduce the risk of acute pancreatitis induced by hypertriglyceridemia [26].

However, when tamoxifen is suspected to be the etiology of pancreatitis, then it should be interrupted and an alternative treatment should be considered [24, 27].

## CONCLUSION

Acute drug-induced pancreatitis is a rare entity, with a pathophysiology that remains poorly understood.

Since the diagnosis is sometimes difficult, an exhaustive assessment is required before selecting the drug in question, which in this case must be stopped permanently.

Hypertriglyceridemia with tamoxifen remains a little-known complication, seen mainly in dyslipidemic patients or with a family history of dyslipidemia, and in rare cases in normolipid patients. This underlines the interest of checking the lipid profile of each patient during this treatment.

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