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Case Report

Liver Failure Letrozole-Induced, Case Report and Review of the Literature

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Abstract

Goals: Letrozole is an aromatase inhibitor widely used as an anti-estrogenic therapy for breast cancer in patients expressing estrogen and/or progesterone receptors. There is currently no data that places it as a potentially hepatotoxic drug. So far, this is the first reported case of Letrozole-induced liver failure in a woman with breast cancer, so we consider the publication of this case of profound impact.

Methods: We describe an extremely rare case of a patient with breast cancer, who presented hepatic failure after 1 month of treatment with neoadjuvant letrozole.

Results: A 75-year-old woman with an oncologic diagnosis of breast cancer, clinical-stage IIA (T2N0M0), a biopsy showed an infiltrating ductal carcinoma without a specific pattern, Estrogen Receptors (ER), positive HScore 300 (sp1), Progesterone Receptors (PR) positive, HScore 160 (1E2), HER2 negative (sp6) and KI67 2% (4b5). Computed Tomography (CT) was negative for metastatic disease. The treatment decision was neoadjuvant therapy based on letrozole 2.5 mg/day. One month after treatment was begun; the patient presented with icteric syndrome. The patient was hospitalized for study protocol. She denied any foreign travel, concomitant alternative, and allopathic medication, as well as alcoholic beverages consumption; there was no history of transfusion or exposure to myelotoxic substances. Obstructive, infectious, and metastatic causes were ruled out.

The patient developed liver failure manifested by grade II encephalopathy and grade III ascites; and received only supportive care.

Conclusions: Liver damage by letrozole is a rare event, but can have fatal consequences, so monitoring liver function during its use is of utmost importance.

Keywords: Breast cancer; Letrozole; Liver failure

Introduction

Drugs Induced Liver Disease (DILI) is a frequent diagnosis of exclusion in patients with acute liver injury without a clear cause or etiology. In 2011, three criteria were proposed to define DILI. 1) ALT (Alanine aminotransferase) elevation >5 ULN (Upper Normal Limit), 2) ALP (Alkaline Phosphatase) elevation >2 ULN accompanied by elevation of GGT (Gamma-Glutamyl Transferase) concentrations in the absence of known bone pathology to justify the increased ALP, 3) Increased ALT >3 ULN with simultaneous increase in Total Bilirubin (TB) concentrations >2 ULN. Clinical are wide, may simulate acute liver failure with severe encephalopathy, acute hepatitis with or without jaundice, and chronic hepatitis with symptomatic or asymptomatic elevated liver function tests [1,2].

There are three types of DILI: Direct, idiosyncratic, and Indirect; direct being the most common type, is usually caused by drugs already known to be toxic to the liver, i.e. drugs whose injury is common and predictable; idiosyncratic injury occurs with drugs that have little or no known toxicity and cause liver damage only in rare cases; and finally, indirect injury is caused by the action of the drug in the body rather than by its idiosyncratic or toxic properties; this type of hepatotoxicity may represent a new hepatic involvement such as immune-mediated hepatitis or the exacerbation of a pre-existing hepatic damage [3-5].

The following is the case of a patient with Breast Cancer, clinical stage (BC) IIA, who presented hepatic failure after 1 month of treatment with neoadjuvant letrozole.

Methods

We describe an extremely rare case of a patient with Breast Cancer, clinical stage (BC) IIA, who presented hepatic failure after 1 month of treatment with neoadjuvant letrozole.

Case Presentation

A 75-year-old woman with history of systemic arterial hypertension of 10 years of evolution treated with enalapril and an oncologic diagnosis of breast cancer, clinical-stage IIA (T2N0M0), a biopsy showed an infiltrating ductal carcinoma without a specific pattern, SBR (Scarf-Bloom-Richardson) scale of 5 (2+2+1), moderate desmoplasia and lymphoplasmacytic infiltrate, without lymphovascular or perineural infiltrate, Estrogen Receptors (ER), positive HScore 300 (sp1), Progesterone Receptors (PR) positive, HScore 160 (1E2), HER2 negative (sp6) and KI67 2% (4b5). Computed Tomography (CT) was negative for metastatic disease. The treatment decision was neoadjuvant therapy based on letrozole 2.5 mg/day. One month after treatment was begun; the patient presented an icteric syndrome.

The patient was hospitalized for study protocol. She denied any foreign travel, concomitant alternative and allopathic medication, as well as alcoholic beverages consumption; there was no history of

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transfusion or exposure to myelotoxic substances. Blood samples were taken: LDH (Lactate Dehydrogenase) 320 IU/L (normal value (VN) 120 IU/L - 240 IU/L), GGT (Gamma-Glutamyl Transpeptidase) 222 IU/L (VN 12 IU/L-58 IU/L), AST (Aspartate Aminotransferase) 1394 IU/L (VN 15 IU/L-46 IU/L), ALT (Alanine Aminotransferase) 1307 IU/L (VN 0 IU/L-35 IU/L), TB (Total Bilirubin) 11.07 mg/dL (VN 02 IU/L-1.3 mg/dL), DB (Direct Bilirubin) 9.02 mg/dL (VN 0 IU/L-0.3 mg/dL), IB (Indirect Bilirubin) 2.05 mg/dL (VN 0 IU/L-1.1 mg/dL), ALB (Albumin) 3.8 g/dL (VN 3.5 IU/L-5 mg/dL), Leukocytes 4.99 thousands/mm^3 (VN 4 thousands/mm^3-12 thousands/mm^3), Hemoglobin 14.5 gr/dL (VN 12.5 gr/dL-16.5 gr/dL), Platelets 211 thousands/mm3 (VN 150 thousands/mm^3-450 thousands/mm^3), Creatinine 0.55 mg/dL (VN 0.71 mg/dL), PT (Prothrombin time) 13.7 sec (9.4 sec-13.5 sec), viral profile HCV (Hepatitis C Virus), AgSHb (Hepatitis B Virus surface antigen) and HIV (Human Immunodeficiency Virus) negative. ANA (Antinuclear Antibodies) positive 1:360.

Metastatic disease and structural alteration were excluded by a liver and biliary tract ultrasound (Figure 1), Computed Tomography (CT), and endoscopic retrograde cholangiopancreatography.

Treatment with letrozole was suspended due to suspicion of DILI. Follow-up on continue as an outpatient basis.

Given the limitations of continuing neoadjuvant treatment, she underwent to conservative surgery with sentinel node biopsy, pathology reported an infiltrating ductal carcinoma, SBR of 5 (2+2+1), moderate desmoplasia and scarce lymphoplasmacytic infiltrate (1%), tumor size 2.5 cm × 0.6 cm, lymph node without evidence of neoplastic cells, RE HScore 300 (sp1), RP HScore 160 (1E2), HER2 negative (sp6) and KI67 2% (4b5). She did not receive adjuvant treatment or radiotherapy.

Two months after discontinuation of letrozole, the patient persists with alteration in liver function tests (TB 3.76 mg/dL, DB 1.99 mg/dL, IB 1.77 mg/dL, GGT 463 IU/L, AST 971 IU/L, ALT 467 IU/L and ALP 230 IU/L). Table 1 summarizes the laboratory findings (Table 1).

A percutaneous ultrasound-guided liver biopsy was performed, which reported liver parenchyma with chronic inflammatory infiltrate of severe lymphohistiocytic predominance with eosinophils in limiting plaque and lobular activity, with individual necrosis of hepatocytes, balonoid degeneration, and intracytoplasmic cholestasis; findings compatible with toxic drug damage (Figure 2). The gastroenterology service concluded a diagnosis of immune-mediated liver damage caused by letrozole. It was decided to withdraw letrozole therapy definitively, as well as other drugs like tamoxifen. Oral corticosteroids and vitamin K were started.

The patient developed liver failure manifested by grade 2 encephalopathy (West Haven scale) and grade 3 ascites and received only supportive care. Patient was lost of follow-up.

Discussion

Aromatase inhibitors are the cornerstone treatment in those patients with hormone-sensitive breast cancer, either in the adjuvant or metastatic setting; therefore, this case is of great clinical interest.

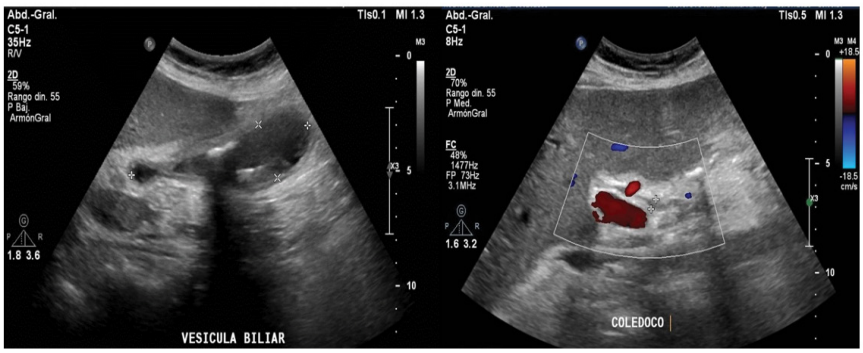

Figure 1: Ultrasound of liver and biliary tract. Gallbladder with oval morphology, longitudinal axis measures 9.6 cm, wall thickening measures 6 mm, multiple hyperechoic images are identified that project acoustic shadow corresponding to gallstone whose diameters range from 6 mm to 16 mm, free gallbladder neck. Intrahepatic and extrahepatic biliary tract caliber is regular.

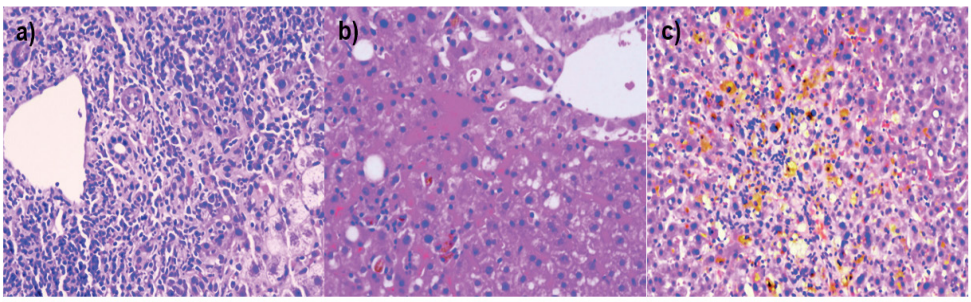

Figure 2: Ultrasound-guided percutaneous liver biopsy. a) A portal space is observed at 40x where the interstitium is expanded by a chronic inflammatory infiltrate where plasma cells predominate. However, there is no activity in the interphase. In addition, we can see a lesion on the ducts, b) It is observed in the interstitium of the lobule infiltrated by lymphocytes and plasma cells, in addition to bile plugs, c) In this picture, the lobular infiltrate is more accentuated, where there is an acute infiltrate. There are also many bile plugs and macro and microvesicular steatosis.

Table 1: Evolution of laboratory tests.

LET	Basal-Letrozole begins	Month 1-EUS-Letrozole suspension		Month 2-Control labs		Month 4 Control labs	Month 5 -Steroid treatment begins-Control labs		Month 7-Hepatic encephalopathy-Control labs	
TB (mg/dL)	0.4	11.01	11.01	17.8	15.81	1.71	12.81	9.53	4.44	2.51
DB (mg/dL)	0	9.02	8.61	15.06	13.22	0.37	10.52	7.55	2.97	1.5
IB (mg/dL)	0.04	2.05	2.4	2.74	2.59	1.34	2.35	1.98	1.47	1.01
AST (U/L)	85	1394	1107	1160	936	859	569	435	106	74
GGT (U/L)	109	222	164	151	171	488	171	167	131	115
ALT (UL)	86	1307	882	621	527	526	444	374	115	82
ALB (gm/dL)	4.5	3.8	2.9	3.7	3.5	3.3	3.1	2.3	2.7	2
ALP (U/L)	92	148	109	142	141	238	153	123	158	110
PT (sec)	13.8	13.7	-	11.2	13.8	12.6	16.9	19.3	14.1	15.6
APTT (sec)	36.9	39.4	-	33.9	36.9	38.2	35.8	37.4	33.2	28.1

*LFT: Liver Function Test; *EUS: Endoscopic Ultrasound; TB: Total Bilirubin; DB: Direct Bilirubin; IB: Indirect Bilirubin; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transpeptidase; ALT: Alanine Aminotransferase; ALB: Albumin; ALP: Alkaline Phosphatase; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time

The present case developed liver toxicity after the first month of treatment with letrozole, characterized by a persistent cholestatic pattern. Imaging studies and laboratory tests ruled out other possible etiologies. The diagnosis of immune-mediated DILI (Drug-Induced Liver Injury) was concluded, supported by the Roussel Uclaf Model (RUCAM score) obtaining 7 points and confirmed by liver biopsy [6].

DILI is a rare entity associated with significant morbidity and mortality, so the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) created LiverTox, a resource to supply information on the diagnosis, cause, frequency, clinical patterns, and management of drug-attributable hepatotoxicity. The drugs reported to be most often associated with DILI are amoxicillin-clavulanic acid, isoniazid, nitrofurantoin, trimethoprim-sulfamethoxazole, and diclofenac. It is convenient to mention that the patient had been taking enalapril for ten years without clinical alteration and with regular laboratory tests. Concomitantly with letrozole she only took it for one month, and until now, there are no reports of drug interaction between both drugs.

On the other hand, in the LiverTox, there are no reports of DILI secondary to enalapril. It only has been reported elevation of transaminases in 2% of the cases that remit in one or two weeks of spontaneous form being the hepatocellular pattern associated to greater severity; nevertheless, in this case, a cholestatic pattern is seen being clear the temporary association between the beginning of the therapy with letrozole and the symptoms of a hepatic lesion [7].

DILI is divided into three groups: direct, idiosyncratic, and indirect. The direct group is the most common type. Direct injury is explained as the one that is caused by drugs already known to be hepatotoxic, for example, drugs whose injuries are common and predictable. In this injury, there is a latency period with a general onset period ranging from 1 to 5 days after the administration of supra-therapeutic doses. For instance, an accidental or intentional overdose can cause this event. This type of injury is characterized by elevated ALT or ALP concentrations without hyperbilirubinemia, with minimal or no symptoms. Values usually normalize upon discontinuation or reduction of the drug dose. Acute hepatic necrosis is the most common form of clinically clear direct hepatotoxicity. Histopathological studies show centrilobular or panlobular necrosis with less inflammation [5].

Idiosyncratic injury occurs with drugs that have little or no known toxicity and cause liver damage only in rare cases. Idiosyncratic injury is unpredictable, is not dose-dependent, and is not reproduced in animal models. It is classified as hepatocellular, cholestatic, or mixed, with hepatocellular hepatitis being the most common pattern. It usually occurs approximately 1 to 2 weeks to 2 to 3 months from the initiation of drug therapy. Symptoms resemble acute viral hepatitis, manifested by large elevations of ALT without a significant increase in ALP. The histopathologic study also shows changes suggestive of acute viral hepatitis with prominent eosinophils [3-5,8].

Finally, indirect injury is caused by the pharmacodynamics of the drug in the organism rather than by its idiosyncratic or toxic properties; this type of hepatotoxicity can stand for a new hepatic involvement such as immune-mediated hepatitis or the exacerbation of a pre-existing hepatic involvement.

The previously mentioned case presents a mixed (idiosyncratic and indirect) type of letrozole-induced hepatic injury, due to enzymatic alterations with cholestatic pattern and due to the elevation of antinuclear antibodies.

Letrozole is a specific non-steroidal aromatase inhibitor. The highest levels of aromatase are found in the ovary and placenta. However, aromatase is also found in other tissues, such as the liver, kidneys, adrenal glands, brain, muscle, and subcutaneous fat, where it is also active in estrogen production, albeit at low levels. This drug is widely used in the context of hormone-sensitive breast cancer in both adjuvant and metastatic settings.

Letrozole-induced liver damage is a rare entity of unknown etiology, reported in approximately 1% of people exposed to the drug. It usually manifests with a mild, transient, and asymptomatic elevation of transaminases, which does not require dose adjustment. However, some case reports of AI-immune-mediated liver damage (mainly by anastrozole and exemestane), with a more abrupt course and associated with acute liver failure, which can lead to fatal consequences. The mechanism by which letrozole causes liver failure is unknown. This drug is metabolized by CYP450 and is a potent inhibitor of CYP2A6. It is a belief that liver damage by letrozole may be increased because of the formation of immunogenic or toxic metabolites [7].

Differentiating between drug-induced hepatitis and autoimmune hepatitis is a challenge for the clinician since these patients did not often present an earlier episode of hepatotoxicity and may share biochemical alterations such as ANAS elevation and insidious course. The biopsy data such as the time of exposure to the drug, and the patient's age can guide us on the diagnosis.

Conclusion

Letrozole is a drug widely used in breast cancer treatment. Liver damage by letrozole is a rare event, but can have fatal consequences, so monitoring liver function during its use is of utmost importance. The present case developed liver damage by indirect (immune-mediated) and idiosyncratic mechanisms. Therefore, the patient developed irreversible liver failure.

Conflict of Interest

The authors have stated that they have no conflicts of interest.

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