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Drug-Induced Liver Injury (DILI) in Luminal B/Her2-Enriched Breast Cancer Patient during Adjuvant Trastuzumab: Case Report and Literature Review

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Abstract

Trastuzumab is a humanized monoclonal antibody used to treat some types of Breast Cancer (BC), including advanced, relapsing or metastatic, specifically in BCs in which the Human-Epidermal Growth Factor Receptor2 (HER2/neu) protein is overexpressed. The anti-HER2 therapy with Trastuzumab is generally well tolerated and the most frequent adverse effects are hypersensitivity reactions and cardiotoxicity, whereas liver toxicity is reported occasionally in literature, being mainly related to Antibody Drug Conjugates (ADCs), like Trastuzumab Emtansine.

We present here a case report and the correlated literature review of a Luminal B/HER2+ BC patient who experienced an important liver toxicity due to Trastuzumab in the adjuvant setting. The cause-effect relationship has been analyzed and demonstrated by the time correlation, AST/ALT trend, exclusion of other causes of liver damage and reappearance of hepatotoxicity at Trastuzumab rechallenge. The hepatotoxicity led to permanent treatment discontinuation. Careful monitoring of liver function during Trastuzumab therapy is so far needed to identify early hepatotoxicity that can be severe for the patient.

Keywords: Breast cancer; Hepatotoxicity; Trastuzumab

Introduction

Four subtypes of invasive carcinoma have been identified till now, based on the different expression of hormone (ER/PgR) and HER2/neu receptors: Luminal A (lower ki67, strong ER/PgR expression, HER2 negative),

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Luminal B (higher ki67, lower levels of ER/PgR expression), HER2-enriched and Basal-like (Triple Negative Breast Cancer, TNBC).

Luminal B tumors can be distinguished in HER2-negative and positive. The Luminal B/HER2+ tumors are characterized by ER positivity, HER2 positivity or overexpression, any value of Ki67 and any value of PgR.[1]

HER2-overexpressed invasive BC account for 15%-20% of the total and have a worse prognosis than the HER2-negative counterparts.[2] HR+/HER2+ tumors have a better prognosis as compared to HR-.[3]

The HER2 overexpression or amplification allows the use of specific treatments beyond hormonal therapy: Trastuzumab is a humanized monoclonal antibody against the extracellular domain of Epidermal Growth Factor Receptor 2 (HER2). With his linkage it blocks the activity of this receptor and consequently the cell growth and proliferation.

The blockade of HER2 with Trastuzumab has been shown to improve outcomes for HER2-positive breast cancer population in neoadjuvant, adjuvant and metastatic settings.

Patients with early-stage HER2-positive breast cancer derive substantial survival benefit from adjuvant Trastuzumab in combination with chemotherapy.[4]

Trastuzumab is usually well tolerated: it is not associated with the adverse events that typically occur with chemotherapy (alopecia, myelosuppression, nausea). Its most frequent adverse effects are hypersensitivity reactions and cardiotoxicity (principally congestive heart failure).[5]

DILI (Drug-Induced Liver Injury) represents an insult to the liver by various compounds ranging from medications to herbal supplements. Chemotherapeutic agents are relatively rare reported causes of DILI, because the liver injury during a treatment in an oncologic patient can be related to a lot of factors: other potentially hepatotoxic medications, infections or metastatic involvement of the liver. For this reason, DILI by chemotherapeutic agents is often under-reported.[6]

Trastuzumab is not typically associated with liver injury, but since its approval and wide scale use, there have been some reports of DILI that occur after 1 to 8 cycles of therapy. Due to this reason Trastuzumab is considered by LiverTox in Class D (possible rare cause of clinically apparent liver injury).[7]

Here we present a case report of a Luminal B/HER2-enriched patient who experienced an important hepatotoxicity caused by Trastuzumab administration in the adjuvant therapy.

Case Report

The patient was a 51-year-old perimenopausal Caucasian woman with no significant comorbidities, apart from controlled hypertension, on treatment with Furosemide 1 cp/die and Enalapril 1 cp/die.

The patient complained of a mass in her right breast in December 2020. She got a breast ultrasound that showed in her right breast a nodular area of 30 mm in UOQ (biopsied) and multiple hypoechoic areas of 7 mm and 15 mm in LOQ. At the axillary ipsilateral cord there was an oval lymph node with thickened cortex of 10 mm × 6 mm.

The core needle biopsy revealed an invasive ductal carcinoma, G2. The molecular profile was ER+ (80%) PgR+ (60%), intermediate Ki67 value (25%) and HER2 overexpressed (3+). A fine needle aspiration of the lymph node confirmed the presence of cancer cells.

Considering the extension of the disease (cT2N1M0) and the molecular profile, the patient was a candidate for neoadjuvant therapy with Paclitaxel 80 mg/mq + Trastuzumab 4 mg/kg (loading dose) and 2 mg/kg (subsequent

doses) weekly for 12 weeks followed by Epirubicin (90 mg/mq) and Cyclophosphamide (600 mg/mq) for 4 cycles.

In February 2021, before the start of the treatment, an isolated AST/ALT alteration (42/73 U/L) was found. Hepatitis tests were performed: HAV and HCV serology was negative, and the patient was HBV vaccinated. On the recommendation of a hepatologist, some thorough exams were performed: ANA (Antinuclear Antibodies) were 1:1280 and AMA (Anti-Mitochondrial Antibodies) were 1:1280; ASMA (Anti-Smooth Muscle Antibodies), anti-LKM antibodies, Anti-Proteinase-3 antibodies and anti-Myeloperoxidase antibodies were negative. Lipid profile, blood iron levels and ceruloplasmin were normal and there wasn't alpha-1 antitrypsin deficiency.

An abdominal echography and a CT were performed and they were normal. The patient underwent a FibroScan Testing, which showed a Steatosis Grade S1 (CAP 257), but not fibrosis.

Related to positivity to ANA and AMA finding, a completed antibody panel was indicated: Anti-Mitochondrial Antibodies M2 and anti-M2-3E were positive.

The case was discussed with the hepatologist: the AMA positivity suggested a diagnosis of primary biliary cholangitis (CBP) although the cholestasis indexes (ALP and GGT) were within the normal ranges. The patient started Ursodeoxycholic Acid (UDCA) therapy with hepatic function monitoring.

The treatment with paclitaxel was started at 80% of the total dose, according to the hepatologist indication, with monitoring of liver function tests that spontaneously normalized. Starting with the third cycle, she continued with a full dose of Paclitaxel.

From February 2021 to August 2021 the patient received neoadjuvant treatment with Paclitaxel + Trastuzumab weekly for 12 cycles followed by Epirubicin and Cyclophosphamide for 4 cycles. The treatment was well tolerated.

Considering the premenopausal status, she also started LHRH analogue (Decapeptyl 3.75 monthly).

At the restaging breast ultrasound done before surgery, there was a partial disease response to the neoadjuvant treatment: the nodular area in UOQ was no longer recognizable and the multiple areas of increased enhancement in LOQ have been numerically and dimensionally reduced. Also the lymph node reported was reduced.

Because of the multicentric and multifocal breast cancer, in September 2021 the patient underwent total right mastectomy and BLS and the pathological diagnosis was multifocal invasive ductal carcinoma. There was evidence of a partial response to the therapy, but residual cancer > 50% of the tumor. The molecular profile was ER 60%, PgR 5%, Ki67 5%, HER2 3+. Micrometastases were present in one lymph node and ITC (Isolated Tumoral Cells) in two sentinel lymph nodes. Final stage was yp(m) T1cypN1mi (sn) (pTNM AJCC 8th ed.).

Due to the staging, and the biology, the patient was considered eligible for adjuvant therapy with TDM-1, in the KATHERINE trial, in addition to hormonal therapy with Exemestane and LHRH analogue.

During the post-surgery staging, a chest CT scan revealed some pulmonary micronodules and hilar adenopathies. The patient underwent a bronchoscopy and endo bronchial ultrasound, the needle aspiration was negative for CTM. The case was discussed with pneumologists and it was suggestive of sarcoidosis. The adenopathies and pulmonary micronodules remained stable in the following controls.

In November 2021, the patient started TDM-1 treatment. After a few minutes of administration, she had an infusion reaction with hypertensive peak, chills, desaturation and thoracic pain. In the following days the patient complained of pressure rise, tachycardia, lumbar pain and dry cough.

Due to the adverse reaction to TDM-1 it was prudently decided to continue only with Trastuzumab, together with Exemestane started in December 2021.

Starting from April 6th 2022, after 5 cycles of Trastuzumab, AST/ALT values progressively increased, reaching the highest value of 261/580 UI/L (Grade 3) in two weeks, with normality of other hepatic indexes.

The treatment was discontinued and the patient underwent thorough exams: HAV, HBV, HCV and HEV serology were negative, as well as CMV and EBV nucleic acids, whereas EBV and CMV serology demonstrated a previous infection. Liver ultrasound was performed showing a mild steatosis; an abdomen CT was also performed, resulting in normal parameters. In the suspicion of an overlap syndrome of CBP/HAI (Autoimmune hepatitis), other autoimmunity tests were performed, showing negativity for the presence of ANA 1:1280 with mitochondrion-like pattern, AMA-M2 and M2-3E. Sp100, PML, gp210, LKM-1, LC-1, SLA/LP, Ro-52 were absent.

The patient was evaluated by a hepatologist: the clinical picture indicated a possible DILI (Drug Induced Liver Injury) by Trastuzumab overlapped on a setting of primary biliary cholangitis (AMA+) and metabolic syndrome (hypertension, OSAS, Obesity Grade 1 and dyslipidemia), not known at treatment start.

Considering DILI potentially caused by both Trastuzumab and Exemestane, these drugs were stopped.

Gradually, AST/ALT decreased in about 6 weeks, so far there was not an absolute hepatological contraindication for Trastuzumab rechallenge, because DILI was not severe (bilirubin and coagulation values within the normal ranges) and there was no certainly that the drug was the cause of toxicity with the reintroduction of Trastuzumab and Exemestane.

In agreement with hepatologist, on August 8th 2022 the patient resumed treatment under the restriction of with weekly hepatic function monitoring; however, hepatotoxicity again recurred after the first re-administration (Figure 1).

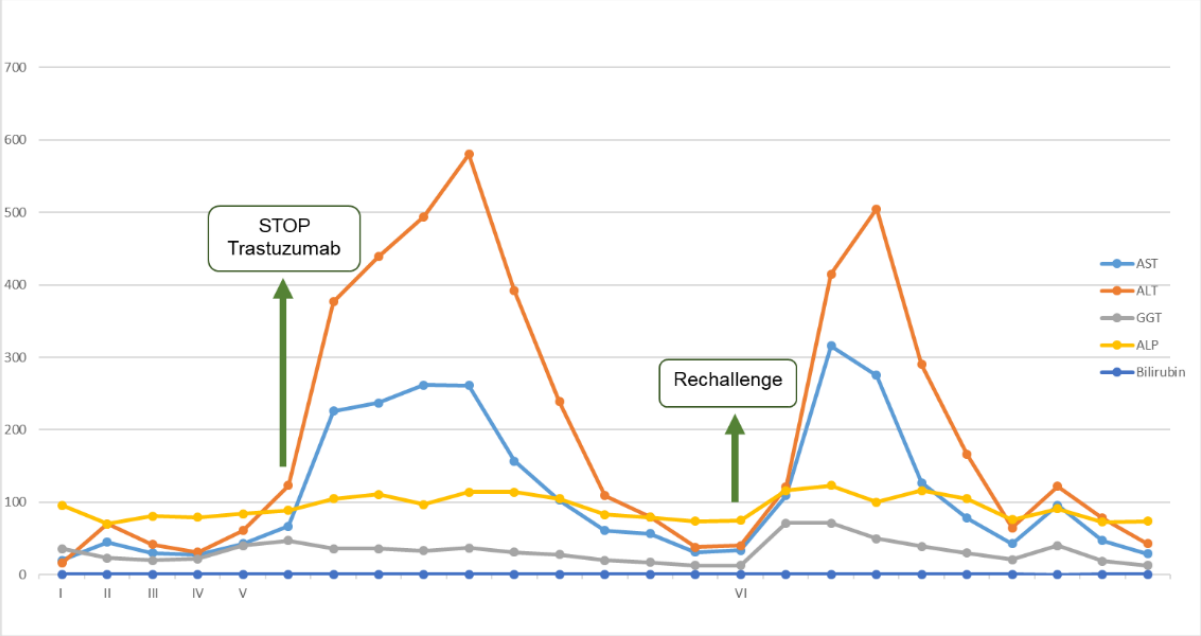

Figure 1: Trend of hepatic function of the patient during adjuvant treatment with Trastuzumab.

In consideration of the difficult differential diagnosis which included a potential liver toxicity by Trastuzumab, a possible primary biliary cholangitis and hepatic steatosis in a patient affected by metabolic syndrome, and a seronegative autoimmune hepatitis, the hepatologist provided indication to perform a liver biopsy.

The liver biopsy showed inflammatory infiltrate in many of the portal spaces mainly of lymphohistiocytic type with a plasma cell component, from mild to moderate/severe, which attacks the limiting plate in some spots. Non-necrotizing epithelioid granulomas have been seen in two triads. Interlobular bile ducts are recognisable with discrete inflammatory infiltrate, showing architectural distortion. Hepatocyte laminae were irregular due to the presence of multiple necroinflammatory phenomena. The diagnosis was acute moderate/severe hepatitis caused by pharmacologic damage associated with chronic focal non-destructive cholangitis with non-necrotizing portal and intracinar granulomatosis. It was impossible to distinguish between a primary biliary cholangitis, a hepatic localization of pulmonary sarcoidosis, or an overlap of both diseases (Figure 2).

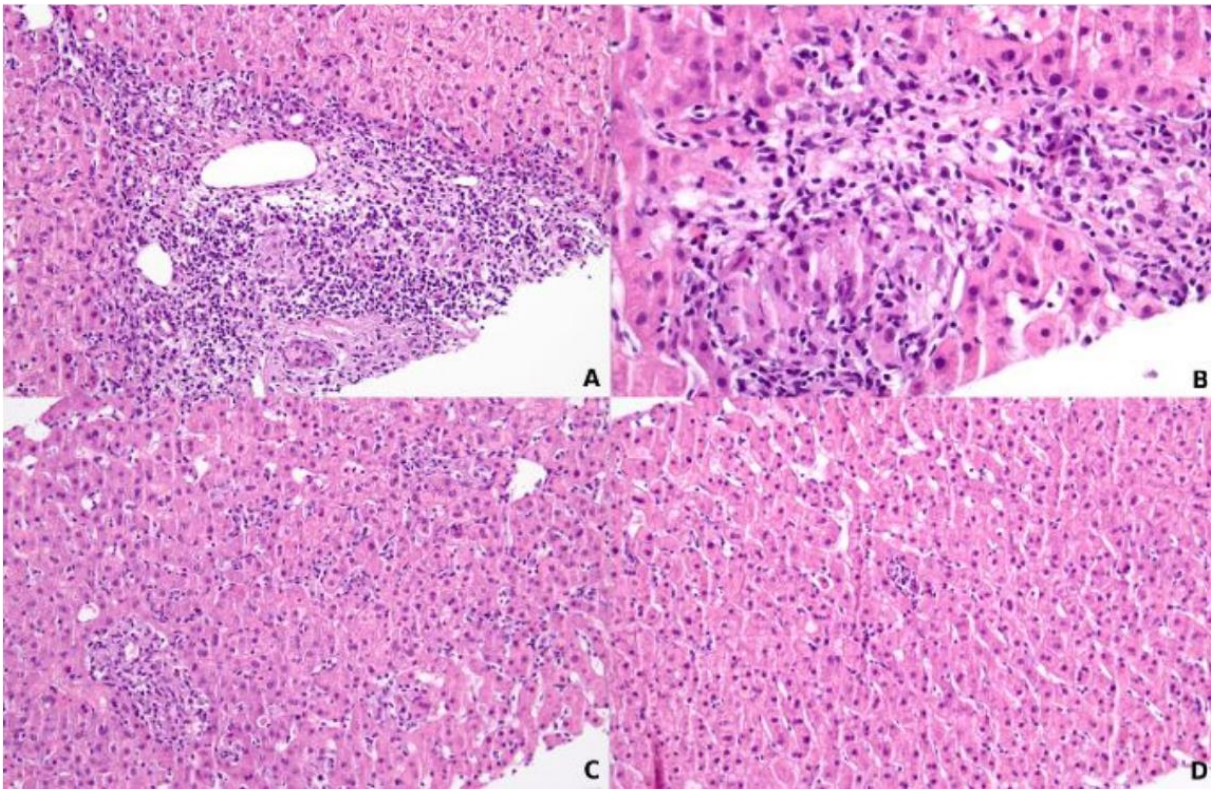

Figure 2: A) Portal tract inflammation with lymphocytes and plasma cells infiltrating the limiting plate (H&E 10x). B) Non-necrotizing granuloma (H&E 40x). C) Acinar multiple necroinflammatory foci (H&E 10x). D) Acinar spotty necrosis, with apoptotic bodies (H&E 10x).

In consideration of Trastuzumab-induced DILI and hepatic relapse with rechallenge, the definitive hepatological diagnosis was DILI by Trastuzumab in a patient with primary biliary cholangitis, metabolic syndrome and a possible liver involvement by pulmonary sarcoidosis. There was an absolute contraindication to continue anti-HER2 treatment.

The patient also stopped the hormonal treatment with Exemestane.

She continued hepatologic and oncologic follow-up.

Discussion

The HER2 gene encodes a tyrosine kinase transmembrane receptor and its amplification or overexpression, which occurs in about 13%-15% of breast cancers, makes cancer cells grow and proliferate more quickly, so the breast cancer HER2-enriched is associated with a poor prognosis.

HER2-enrichment is also a predictor of response to target therapy with anti-HER2 agents, such as Trastuzumab, which have changed the cure prospects in breast cancer HER2 enriched in adjuvant, neoadjuvant and metastatic settings, with great results and longer responses.[2,8,9]

Treatment with Trastuzumab is generally well tolerated, in fact it has been associated with maintenance of health-related quality of life. In the final analysis of the HERA trial safety analysis was a secondary endpoint: after 11 years' follow up no new safety concerns have emerged since previous reports. The most frequent Adverse Effects (AEs) of Trastuzumab remain hypersensitivity reactions and cardiotoxicity, principally congestive heart failure.[5]

The hypersensitivity reactions occur with the administration of the first infusion and present with fever, chills, pain, asthenia, nausea, vomiting, and headache. Between 20% and 40% of women have an infusion reaction that is often mild. Only 0.3% of patients experienced anaphylaxis. Cardiac dysfunction that manifests as congestive heart failure, cardiomyopathy, and/or a decrease in ejection fraction is a specific AE of anti-HER2 therapies and occurs from 4.1% to 10% of patients treated.[10,11]

Hematologic abnormalities or hepatic laboratory abnormalities are rare: they happen with a frequency of 3%-4% and are usually related to concomitant administration of chemotherapy or disease progression, than a Trastuzumab AE.

The patient we describe experienced a severe liver disfunction related to Trastuzumab administration.

In the literature some other cases of trastuzumab-induced hepatotoxicity are reported.

Ishizuna et al. described a case of HER2 positive breast cancer that developed hepatotoxicity at first during chemotherapy with Epirubicin and Cyclophosphamide, then after administration of Trastuzumab (4 mg/kg) in a neoadjuvant setting. Trastuzumab was discontinued and the patient continued Paclitaxel in monotherapy until surgery. The patient did not have liver disease, take drugs or have hepatitis B or C infection. The diagnosis of trastuzumab-induced hepatotoxicity was formulated on the basis of timing and the Drug-induced Lymphocyte Stimulation Test (DLST), which revealed a positive reaction to trastuzumab (stimulation index: 227%).[12]

Muñoz et al. reported a case of HER2-positive breast cancer that underwent surgery and adjuvant therapy. The patient developed hepatotoxicity G3 first during chemotherapy and then during Trastuzumab therapy (8 mg/kg). AST/ALT went back to normal values one month after Trastuzumab was discontinued. Therefore, Trastuzumab was reintroduced at 2 mg/kg every week and she completed 1 year of treatment without recurrence of hepatotoxicity. The authors speculated that hepatotoxicity was caused by Trastuzumab in a dose-dependent manner, but chemotherapy-induced hepatotoxicity also probably played a role in trastuzumab-induced hepatotoxicity.[13]

Srinivasan et al. presented a case of HER2-positive breast cancer that underwent neoadjuvant therapy with Doxorubicin and Cyclophosphamide for 4 cycles, well tolerated, and then weekly Paclitaxel and Trastuzumab. Hepatotoxicity occurred after 5 cycles and increased until the 8th cycle, when, being the patient symptomatic, the treatment was discontinued. The same effects occurred in the adjuvant setting, after surgery, with rechallenge of trastuzumab. The patient was hepatitis C antibody- and elevated RNA- positive. A liver biopsy was performed, showing mild portal inflammation and mild interface hepatitis. The authors, from the strong temporal association, concluded that the patient developed DILI caused by Trastuzumab.[14]

Vucicevic et al. reported the case of a patient with HER2-positive breast cancer, who developed hepatotoxicity after 8 cycles of Trastuzumab. In this patient, the transaminase level continued to increase for 2 months after

Trastuzumab was discontinued. A liver biopsy was performed, which showed acute hepatitis with portal infiltrates comprising lymphocytes, plasma cells and eosinophils. The authors concluded that the patient developed a drug-induced hepatotoxicity, given the time correlation and the long half-life of Trastuzumab.[15]

In all these reports hepatotoxicity was attributed to Trastuzumab administration because of time correlation, return of ALT/AST level to basal values when Trastuzumab was discontinued, exclusion of other causes of liver damage and hepatotoxicity with the re-challenge of Trastuzumab. These are 4 criteria that prove that liver injury is caused by a medication.[16]

However, in these case reports the onset of Trastuzumab-related toxicity was described not only during therapy with Trastuzumab alone, but also during chemotherapy or combination therapy (Paclitaxel-Trastuzumab).

Only the patient described by Vucicevic can be compared with our patient: hepatologic toxicity arised only after the beginning of Trastuzumab therapy.

We can include our patient in a liver injury caused by a drug because of these criteria: hepatotoxicity started after 5 cycles of Trastuzumab and gradually AST/ALT decreased after Trastuzumab was discontinued. No other causes of liver damage (apart from primary biliary cholangitis, which was under hepatologic control) were found and hepatotoxicity recurred with re-challenge.

According to LiverTox Trastuzumab is a possible rare cause of clinically apparent liver injury (Class D).

DILI (Drug-Induced Liver Injury) is defined as liver injury caused by various medications, herbs, or other xenobiotics, leading to abnormalities in liver tests or liver dysfunction with the reasonable exclusion of other etiologies.[20] In particular it is characterized by an elevation in the serum concentration of alanine aminotransferase (ALT) above 5x the Upper Limit of Normal (ULN), or of Alkaline Phosphatase (ALP) exceeding 2× ULN, or the presence of 3x ULN elevation in ALT concentration and simultaneous elevation of bilirubin concentration exceeding 2xULN. These alterations have to appear within 90 days of suspect drug initiation and decrease within one month of drug cessation.[17] The most common clinical presentations of DILI are hepatocellular, cholestatic, and mixed, which should be defined on the basis of biochemical criteria.[18]

The pattern of hepatotoxicity of Trastuzumab is often hepatocellular and it occurs after 1 to 8 cycles.[19]

There are not specific tests to confirm the diagnosis of DILI and the causality assessment is necessary to establish a definitive link between drug intake and liver injury. The diagnosis of a drug reaction must be considered in any patient with liver dysfunction. Some tools can be used (with their limits) to evaluate the causality assessment in DILI: the Roussel Uclaf Causality Assessment Method (RUCAM) and the DILI diagnostic scale.[18]

For the diagnosis other drugs, herbal medications or other substances taken by the patient must be excluded, as well as viral hepatitis and alcohol abuse,[20] and liver injury must recur upon rechallenge of the suspected drug.[17]

Compared with the DILI caused by primary exposition the drug, the rechallenge is associated with a more severe reaction. Björnsson and Hoofnagle have classified some drugs based on their probability to cause hepatotoxicity according to cases reported in literature: Trastuzumab and Exemestane are in category C and D respectively. Category C included agents with about 26% of positive rechallenge; the drugs in category D were implicated in positive rechallenge only in 11% cases.[21]

The diagnosis of DILI is mainly clinical, but liver biopsy can be helpful to exclude other causes of liver disease, although a certain differential diagnosis between DILI and other disease (for example idiopathic autoimmune

hepatitis AIH) is difficult. There are some histological findings that are observed in cases of DILI: interface hepatitis, focal necrosis and portal inflammation. A mild inflammatory infiltrate is seen and is predominantly characterized by polymorphonuclear leukocytes in small aggregates. Another characteristic is the presence of intra-acinar lymphocytes and canalicular cholestasis.[22,23]

Concerning our patient, she did not have a personal or family history of liver disease, except for ANA (Anti-Nuclear Antibodies) and AMA M2 (Anti-Mitochondrial Antibodies) positivity which is related to primitive biliary cirrhosis. This hepatic picture was under hepatologic control and liver function at the beginning of therapy was normal. Liver injury was not related to other drugs and the patient did not have any hepatitis A, B, C or E, EBV or CMV infections.

As described in the literature, hepatologic damage occurred after some Trastuzumab administration (5 cycles) and AST/ALT levels increased during the month after the suspension of the drug.

The final diagnosis for this case was Drug Induced Liver Injury by Trastuzumab, based on the finding that hepatotoxicity developed after 5 cycles of Trastuzumab, gradually AST/ALT decreased after Trastuzumab was discontinued and hepatotoxicity recurred with re-challenge (Figure 1). In the liver biopsy performed we found a picture of acute severe hepatitis that was attributable to DILI, and presence of chronic cholangitis and granulomatosis that could not allow to distinguish between biliary primary cirrhosis or localization of sarcoidosis (Figure 2).

This adverse effect is rare, but it is necessary to monitor hepatic function to detect it early and prevent complications, which could be fatal.

Conclusion

Trastuzumab is a well-tolerated drug that gives very good results in neoadjuvant, adjuvant and metastatic settings. It has some specific adverse effects, the most frequent of which are infusion reactions. Typical but rarer is cardiotoxicity. It can also provoke liver injury in the form of acute hepatitis, which, if not detected in time during the Trastuzumab therapy, can be severe for the patient. Careful monitoring of liver function during Trastuzumab therapy is necessary.

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