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Portal hypertension after prolonged use of trastuzumab emtansine: nodular regenerative hyperplasia with autoimmune features

Hipertensão portal após uso prolongado de trastuzumab entansina: hiperplasia nodular regenerativa com alterações autoimunes

Hipertensión portal después de uso prolongado de entansine trastuzumab: hiperplasia nodular regenerativa com alterações autoinmunes

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Abstract
We report a rare complication associated with prolonged use of trastuzumab emtansine (T-DM1) – a composed therapy for HER2+ breast cancer – presenting with laboratorial autoimmune features that could have delayed the diagnosis or led to misdiagnosis. A 55-year-old female was referred to the hepatologist with a computed tomography suggestive of portal hypertension for etiological investigation. History of invasive ductal carcinoma in the right breast undergoing treatment for 5 years. She had already undergone neoadjuvant chemotherapy, mastectomy, radiotherapy and adjuvant chemotherapy. By the time of metastatic diagnosis, she was in monotherapy with T-DM1 for 2.5 years. Upper endoscopy showed esophageal varices and portal hypertension gastropathy. Laboratorial tests revealed increased transaminases, hypergammaglobulinemia and positive antinuclear antibody. Liver biopsy was performed for autoimmune hepatitis differential diagnosis but revealed nodular regenerative hyperplasia. T-DM1 was discontinued. After a 2-year follow-up, the patient did not present any complications of portal hypertension, although persisted with esophageal varices.
Keywords: Breast neoplasms; Trastuzumab; Hypertension, portal; Hepatitis, autoimmune.

Resumo
Neste relato de caso apresentamos uma complicação rara associada ao uso prolongado de trastuzumab entansina (T-DM1) – uma terapia composta para câncer de mama HER2+ – que ocorreu acompanhada de características laboratoriais autoimunes que poderiam atrasar ou levar a diagnósticos incorretos. Paciente do sexo feminino, 55 anos, encaminhada ao hepatologista com tomografia computadorizada sugestiva de hipertensão portal para investigação etiológica. História de carcinoma ductal invasivo em mama direita em tratamento há 5 anos sendo realizado quimioterapia neoadjuvante, mastectomia, radioterapia e quimioterapia adjuvante. Evoluiu com doença metastática quando estava em uso de monoterapia com T-DM1 há 2,5 anos. A endoscopia digestiva alta mostrou varizes esofágicas e gastropatia da hipertensão portal. Os exames laboratoriais revelaram aumento das transaminases, hipergamaglobulinemia e anticorpo antinuclear positivo. Biópsia hepática foi realizada para diagnóstico diferencial com hepatite autoimune, mas revelou hiperplasia nodular regenerativa. O T-DM1 foi descontinuado. Após seguimento de 2 anos, a paciente não apresentou complicações de hipertensão portal, embora persista com varizes esofágicas.
Palavras-chave: Neoplasias da mama; Trastuzumab; Hipertensão portal; Hepatite autoimune.

Resumen
En el artículo se presenta una rara complicación asociada con el uso prolongado de trastuzumab entansina (T-DM1) – una terapia compuesta para el cáncer de mama HER2 +- que estuvo acompañada de análises de laboratorio que pueden retrasar o conducir a diagnósticos equivocados. Paciente de sexo femenino, 55 años, remitida al hepatólogo con tomografía computada sugestiva de hipertensión portal para el estudio etiológico. Antecedentes de carcinoma ductal invasivo en la mama derecha en tratamiento desde hace 5 años, ya sido sometida a quimioterapia neoadyuvante, mastectomía, radioterapia y quimioterapia adyuvante. Después del diagnóstico de enfermedad metástasica, en el momento de la consulta, la paciente se encontraba en monoterapia con T-DM1 durante 2,5 años. La endoscopia ha mostrado varices esofágicas y gastropatía por hipertensión portal. Las pruebas de laboratorio han revelado un aumento de transaminasas, hipergammaglobulinemia y anticuerpos antinucleares positivos. Se efectuó la biopsia del hígado para el diagnóstico diferencial con hepatitis autoinmune, pero ha mostrado la hiperplasia nodular regenerativa. T-DM1 que ha sido descatalogado. Luego, un seguimiento de 2 años, la paciente no presentó complicaciones de hipertensión portal, aunque persiste con varices esofágicas.
Palabras clave: Neoplasias de la mama; Trastuzumab; Hipertensión portal; Hepatitis autoinmune.

1. Introduction

Breast cancer was the world's most incident malignant neoplasm in 2018 and the second with the highest mortality rates (Parise, Bauer, Brown, & Caggiano, 2009; Siegel, Miller, & Jemal, 2019). About 20% of breast cancer overexpress HER2, a proto-oncogene that is associated with more aggressive tumors (Parise et al., 2009). Increasing knowledge about the role of HER2 in breast cancer pathogenesis has led to the development of innovative and targeted therapies for HER2+ cancers, such as trastuzumab emtansine (T-DM1). This drug is composed of trastuzumab, a monoclonal antibody that targets HER2 (Romond et al., 2005), and emtansine (DM1), a derivate of maytansine, which is a microtubule polymerization inhibitor (Remillard, Rebhun, Howie, & Kupchan, 1975).

A phase III T-DM1 clinical trial reported progression-free and overall survival improvement when compared with lapatinib and capecitabine therapy (Diéras et al., 2017; Verma et al., 2012). The most commonly described adverse events (AE) related to the drug use were: fatigue (46%), nausea (43%), thrombocytopenia (32%), headache (29%) and constipation (26%), while the most common grade 3 to 4 AE reported were laboratory abnormalities such as thrombocytopenia (12%) and increased AST serum concentration (4%) (Diéras et al., 2014). The AE culminated in 7% of drug discontinuation among the patients and 12 deaths – three of them of hepatic failure (Diéras et al., 2014).

Three cases of biopsy-confirmed nodular regenerative hyperplasia (NRH) were described in the T-DM1 safety analysis study cited (Diéras et al., 2014), all of them with portal hypertension at presentation, with diagnosis in the drug cycle 3, 20 and 37. In one of the patients, the AE resulted in death by liver failure.

According to the VigiBase, the World Health Organization global database of individual case safety reports, 33 cases of NRH were recorded in association to T-DM1 and 37 cases of portal hypertension until the time of this publication. To our knowledge, 13 cases of NRH confirmed by biopsy have been described in literature (Benguerfi, Diéras, Campone, Mosnier, & Robert, 2020; Diéras et al., 2014; Force et al., 2016; Lepelley et al., 2018; Milam et al., 2019). The time between the start of T-DM1 treatment and NRH diagnosis in the reported cases goes from 15 months to four years, all of them manifested by portal hypertension.

NRH is a rare liver condition characterized by benign transformation of hepatic parenchyma into regenerative nodules. It may lead to noncirrhotic portal hypertension (Hartleb, 2011).Since T-DM1 is a commonly used drug in breast cancer therapy, it is important to study its AE, especially because hepatic complications and death by liver causes have already been described associated with NRH secondary to T-DM1. In this case we discuss this rare complication associated with prolonged use of T-DM1 and the presence of autoantibodies and hypergammaglobulinemia, a new feature in the literature which can delay the diagnosis or lead to misdiagnosis.

2. Methodology

The present report, a descriptive qualitative study structured as an empirical analysis of clinical, radiologic and laboratorial aspects as defined by Yin (2015), aims to report a rare adverse event with new diagnostic features, the studies we conducted until reaching the diagnosis and its short-term resolution. The patient signed the Free and Informed Consent Term, authorizing the use of clinical laboratory data and images, taking into account the ethical principles that govern research with human beings present in the Declaration of Helsinki.

3. Case Report

A 55-year-old female was referred to the hepatologist with a computed tomography indicating an increase in the caliber of the portal system vessels with recanalization of paraumbilical veins, suggesting portal hypertension. The patient has a clinical history of invasive ductal carcinoma in the right breast with 5 years of treatment: neoadjuvant chemotherapy (cycles of doxorubicin/cyclophosphamide followed by docetaxel and trastuzumab), total mastectomy, radiotherapy (25 sessions) and adjuvant chemotherapy. After surgery, she initiated trastuzumab and anastrozole, which were substituted by trastuzumab emtansine (T-DM1) because of vertebral and femoral metastases diagnosis. Comorbidities are arterial hypertension, type 2 diabetes mellitus, obesity and dyslipidemia, classic components of metabolic syndrome. She was currently in use of pantoprazole, losartan, metformin and T-DM1 3.6 mg/kg every 21 days on monotherapy for 2.5 years.

Portal hypertension was investigated. Upper digestive endoscopy showed esophageal varices and mild portal hypertensive gastropathy, with normal duodenum. Laboratory tests revealed mildly increased transaminases, hypergammaglobulinemia and fine-speckled antinuclear antibody 1:160 (Table 1).

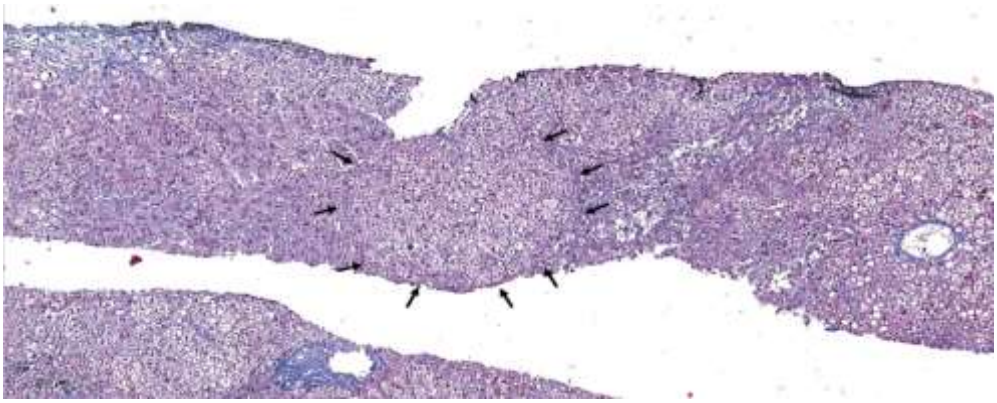
Table 1. Patient Laboratory tests. Mildly increased Alanine transaminase (ALT) and Aspartate transaminase (AST), thrombocytopenia, hypergammaglobulinemia and fine-speckled antinuclear antibody 1:160.

Parameter	Reference value	Before interruption	24 months after interruption
AST (U/L)	< 32	48	33
ALT (U/L)	< 31	34	49
AP (U/L)	< 120	100	-
GGT (U/L)	< 38	61	124.3
Platelets (10^9/mm^3)	> 150	139	202
Gamma Globulin (g/dL)	< 1.75	2.15	1.47
Viral Hepatitis Serology	Negative	Negative	-
Antimitochondrial Antibody	Negative	Negative	-
Antismooth Muscle Antibody	Negative	Negative	Negative
Antinuclear Antibody	< 1:40	1:160 (fine-speckled)	1:640 (fine-speckled)

Source: Patient laboratory tests.

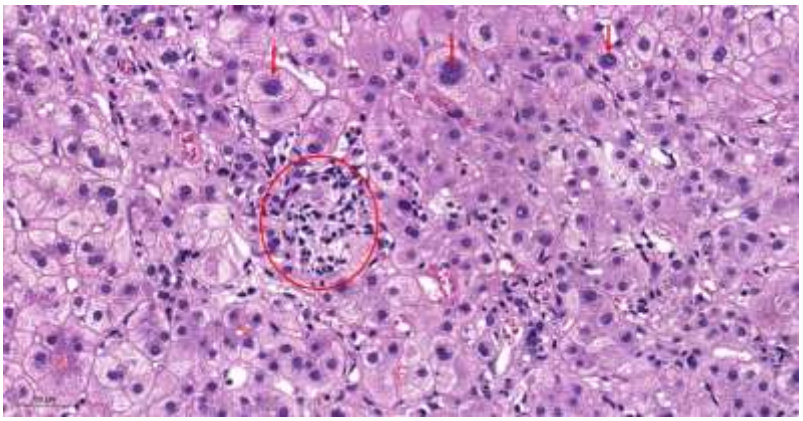
Liver biopsy was performed, which identified diffuse regenerative nodules without parietal thickening of portal venules, and no perisinusoidal or portal fibrosis. Other focal findings were hepatocellular necrosis, ballooned hepatocytes, rosettes and polyploidy. The histopathologic examination was suggestive of NRH (Figures 1 and 2).

Figure 1. Biopsy of the liver stained with hematoxylin, eosin and Masson's trichrome stain. Arrows delimit area of nodular arrangement.



Source: Patient liver biopsy.

Figure 2. Biopsy of the liver stained with hematoxylin, eosin and Masson's trichrome stain showing focal hepatocellular necrosis (circle), ballooned hepatocytes, rosettes (stars) and polyploidy (arrows).



Source: Patient liver biopsy.

After the biopsy results, T-DM1 was discontinued and substituted by fulvestrant and trastuzumab. At 24 months of follow-up after T-DM1 removal, the patient did not present any complications of portal hypertension, although persisted with esophageal varices and computerized tomography with the same portal hypertension signs. Laboratory tests are observed in Table 1.

4. Discussion

Classically, NRH occurs due to heterogeneous hepatic perfusion by portal flow reduction, which results in ischemia, atrophy of hepatocytes and revascularization that leads to nodular hyperplasia of adjacent hepatocytes (Reshamwala, Kleiner, & Heller, 2006). Drug-induced NRH is rare, and its mechanism is still unknown, although it is speculated that it may be related to

venous or sinusoidal damage or even to drug-induced vasculitis. NRH may be asymptomatic for many years, but it can be associated with elevated alkaline phosphatase serum levels and portal hypertension (Reshamwala et al., 2006).

Once laboratory exams are unable to diagnose NRH, imaging examination is needed not only to identify its suggestive features but also to investigate other causes of nodular liver lesions, such as primary liver tumors or secondary neoplastic lesions. Histological evaluation, however, is indispensable for a definitive diagnosis by observation of micronodular transformation of the parenchyma with central hyperplasia, atrophic rim and no fibrosis (Hartleb, 2011).

Although NHR may be associated with common rheumatological conditions that involves vasculitic processes, such as rheumatoid arthritis, there is no clear association between autoimmune markers and NHR itself in current literature.

Under these circumstances, the presence of antinuclear antibodies (ANA) imposes a great challenge as ANA may suggest associated autoimmune liver diseases, however the exam lacks specificity, since even the inflammatory state of metabolic syndrome may favor the occurrence of such antibodies (Blanco, 2017).

Nevertheless, our case becomes more outstanding due to the presence of hypergammaglobulinemia: two other cases of HNR after T-DM1 presented ANA positivity (Force et al., 2016), and one of them also presented antismooth muscle antibody (SMA) (1:40), however, none showed hypergammaglobulinemia.

This finding is remarkable as the combination of hypergammaglobulinemia, increase of aminotransferases and positive ANA raised the hypothesis of autoimmune hepatitis (AH). Biopsy study was performed in order to better assess that differential diagnosis, which, if confirmed, would require specific treatment as it can rapidly evolve with severe liver impairment. Moreover, other autoimmune liver diseases have been associated with NRH at biopsy, such as primary biliary cholangitis (PBC), even though this would not be a suitable diagnosis for this case. Of note, in liver biopsies of 64 patients with early PBC, 43% had some degree of NRH. (Colina, 1992).

Overall, the association between HNR diagnosis, the duration of T-DM1 – greater than that reported in similar cases –, the absence of other etiologies, excluded by liver biopsy, and the apparent interruption in the evolution of the disease after drug discontinuation, corroborates the causal association between the use of T-DM1 and HNR in our patient, even with the autoimmune features.

Even though T-DM1–based regimens are associated with various AE that can result in dose reduction or discontinuation of the drug, it still offers great potential for better efficacy with less toxicity in the treatment of HER2-positive breast cancer (Verma et al., 2012). It has been described that T-DM1 discontinuation can reverse liver test abnormalities and even noncirrhotic portal hypertension (Force et al., 2016). In our case, even though the drug withdrawal did not seem to reverse portal hypertension after 24 months according to image, we observed improvement in platelets that may be related to PH improvement. Furthermore, there was improvement in hypergammaglobulinemia and the patient did not develop complications such as variceal bleeding, ascites and hepatic encephalopathy, which have been described in other patients with drug induced NRH (Benguerfi et al., 2020; Force et al., 2016).

It appears that a high index of suspicion for drug-induced liver injury in patients undergoing treatment with T-DM1 are the best clinical management when faced with portal hypertension and liver test abnormalities. T-DM1 discontinuation seems to be the best therapeutic option, since both portal hypertension resolution and compensation have been observed. Since such complications can lead to discomfort, hospitalization and even death, NRH related portal hypertension treatment is relevant for advanced cancer patients.

5. Final Considerations

Therefore, the reported case represents an uncommon hepatic complication in cancer patients undergoing treatment with targeted HER2+ therapies. The discontinuation of T-DM1 treatment seems to be the best therapeutic option. It is noteworthy that NRH diagnosis is only possible by liver biopsy and may be accompanied by several laboratory changes that hinder its diagnosis, among which are described: antinuclear antibody and antismooth muscle antibody positivity, thrombocytopenia, increased AST serum concentration, among others less frequent. Our patient also had hypergammaglobulinemia. Hepatic nodules and portal hypertension signs observed in images of patients undergoing T-DM1 therapy should always raise suspicion of drug-induced NRH, with or without changes in laboratory tests.

For future researches and works we suggest a more profound analysis involving the associations between the autoimmune markers and NRH and a more structured study to compute the association between the introduction of T-DM1 and the NRH diagnosis. Furthermore, it's mechanism is still unknown, and with the increase in reports of NRH, the study of its physiopathogenesis becomes increasingly imperative.

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