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Elevated liver function tests in a patient with breast cancer

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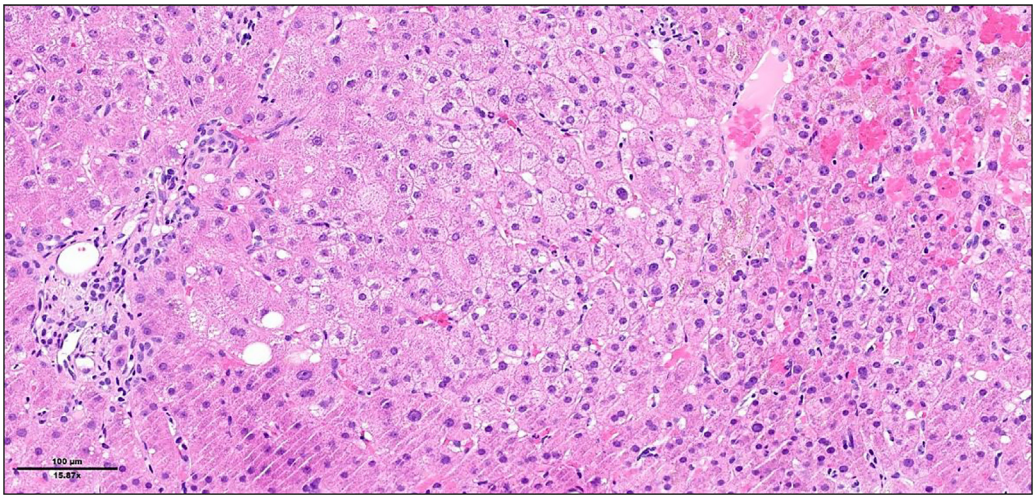

Description

A 49-year-old female was diagnosed with invasive lobular breast carcinoma, grade 3, cT2 cN0 cM0, endocrine resistant and positive for human epidermal growth factor receptor 2 (HER2), in February 2022. She underwent neoadjuvant chemotherapy with 4 cycles of epirubicin and cyclophosphamide followed by 12 doses of weekly paclitaxel combined with trastuzumab and pertuzumab, without liver function test (LFT) elevation. In October 2022, she had tumorectomy followed by adjuvant breast radiotherapy. Due to the absence of complete pathological response, she was started on trastuzumab-emtansine (T-DM1) in November 2022. This treatment was administered at the standard dose of 3.6 mg per kg every 3 weeks for a total of 14 cycles.

After 3 months of treatment with T-DM1, the patient developed mild LFT elevation, with aspartate aminotransferase 59 U/L (normal <32 U/L), alanine aminotransferase 40 U/L (normal <36 U/L), alkaline phosphatase 144 U/L (normal <120 U/L), gamma-glutamyltransferase 156 U/L (normal <42 U/L) and normal total bilirubin. Platelet count was normal (173 G/L). She was asymptomatic. No alterations were seen on abdominal ultrasound. Serologies were negative for viral hepatitis A, B, C and E. Autoantibodies were negative for autoimmune liver disease. Because of persistent LFT elevation a percutaneous liver biopsy was performed (see above).

What is your diagnosis?

- Sinusoidal obstruction syndrome
- Tumoral infiltration
- Porto-sinusoidal vascular disorder
- Cytomegalovirus hepatitis

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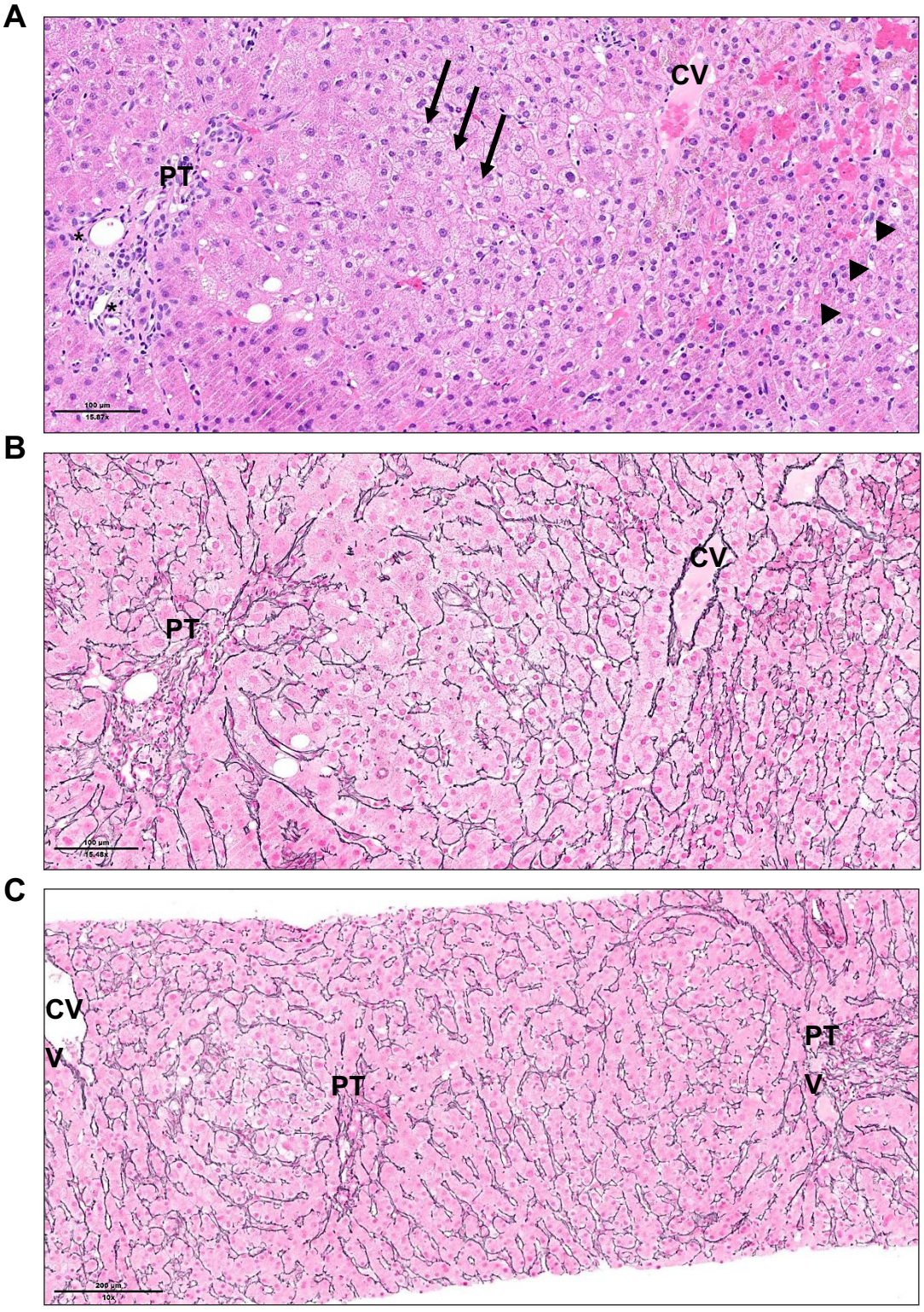

Fig. 1. Liver biopsy findings. (A) Thickened hepatic plates (arrows) alternate with areas of atrophy and congestion (arrowheads). The portal tract contains only small portal vein branches characteristic of portal vein stenosis (asterisks) (hematoxylin-eosin stain). Scale bar, 100 µm. (B) Same area as in panel A with a reticulin stain that demonstrates the alternating size of the hepatic plates. Scale bar, 100 µm. (C) The nodularity of the liver parenchyma is already seen at a lower magnification in this other area of the biopsy. The two portal tracts show either no portal vein branch or a very small one (reticulin stain). Scale bar, 200 µm. CV, central vein; PT, portal tract.

Diagnosis and outcome

A broad diagnostic panel, including PCR for cytomegalovirus, ruled out an infectious cause. Considering the chronology, pattern of LFT elevation and hepatotoxic potential of the oncological treatments, the most likely cause appeared to be drug-induced liver injury. The liver biopsy revealed histological features consistent with nodular regenerative hyperplasia (NRH) and portal vein stenosis (PVS), without any significant portal or lobular inflammation. There was no tumoral infiltration. Although epirubicin, cyclophosphamide and paclitaxel have been associated with sinusoidal obstruction syndrome, the clinical presentation was inconsistent with this condition. Considering the precise chronology and the specific histopathological findings including NRH (previously described in patients receiving emtansine), hepatotoxicity was attributed to T-DM1. Emtansine was discontinued in favor of trastuzumab and pertuzumab combination therapy. The patient continues to be followed, with a progressive decrease in LFTs supporting the diagnosis.

Discussion

Porto-sinusoidal vascular disorder (PSVD) refers to a group of liver vascular abnormalities characterized by lesions of the portal venules and sinusoids. Portal hypertension can develop but may be absent at early stages. Expert liver pathological assessment is crucial for establishing the diagnosis, excluding cirrhosis and showing specific histological findings that include NRH, PVS, or incomplete septal fibrosis.[1]

In our patient, NRH was the dominant pattern, as evident already on the routine hematoxylin-eosin stain and confirmed by the reticulin stain highlighting diffuse micronodularity of the liver parenchyma in the absence of significant fibrosis (Fig. 1). In addition, we also observed features of PVS, characterized by narrowing of the portal vein branch lumen resulting in incomplete to complete disappearance of the vein (Fig. 1).

The spectrum of etiologies and the pathogenesis of PSVD are still incompletely understood. However, chronic infections, thrombophilic, immunological and genetic disorders (such as the short telomere syndrome) as well as certain drugs have been identified as the main causative factors.

Approximately 20% of breast cancers overexpress HER2 and are associated with a more aggressive clinical course. Trastuzumab, a humanized monoclonal antibody targeting HER2, has radically improved the outcome of patients with HER2-positive breast cancer. Trastuzumab conjugated with the microtubule inhibitor emtansine (T-DM1) showed substantial efficacy not only in advanced stage HER2-positive breast cancer but also in the adjuvant setting for patients with residual disease after neoadjuvant chemotherapy comprising trastuzumab.[2] Emtansine is transported into HER2-expressing cancer cells, where it binds to tubulin, disrupts microtubular networks, and results in cell cycle arrest and cell death.[2] The antibody-drug conjugate T-DM1 has been associated with higher rates of adverse effects compared to trastuzumab alone. Importantly, hepatotoxicity leads to drug discontinuation in approximately 3 to 5% of patients.[2] Although the underlying mechanism remains elusive, hepatotoxicity typically manifests as a variable increase in LFTs with an alanine aminotransferase increase of any grade observed in 23.1% of patients.[2]

Several cases of non-cirrhotic portal hypertension have been reported in patients on long-term T-DM1 therapy.[3,4] These patients typically presented with portal hypertension after more than a year of treatment. In these cases, transaminases were generally only mildly elevated. Liver biopsy revealed NRH. Discontinuation of T-DM1 was generally associated with clinical improvement.

In our patient, transaminases were only slightly elevated, consistent with previous reports, and the liver biopsy showed NRH with features of PVS, which, after multidisciplinary discussion, justified discontinuation of T-DM1. At this stage, the patient did not have any evidence of portal hypertension such as reduced portal vein flow, congestive splenomegaly, or collateral circulation based on imaging, which can be explained by the early diagnosis.

In conclusion, long-term T-DM1 treatment may be associated with the development of PSVD and non-cirrhotic portal hypertension even in the absence of marked LFT elevations. Expert liver pathological assessment is crucial for multidisciplinary management and in determining whether to continue, discontinue, or adjust the dose of treatment.

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Conflict of interest

The authors declare no conflict of interest.

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Authors' contributions

Christine Sempoux and Montserrat Fraga selected the clinical case. Cyril Neftel, Christine Sempoux and Montserrat Fraga wrote the manuscript together with feedback from all authors. Christine Sempoux made the figures. Cyril Neftel, Darius Moradpour and Montserrat Fraga were in charge of the hepatological aspect, Christine Sempoux of the pathological aspect, Khalil Zaman of the oncological aspect and Haithem Chtioui of the pharmacological aspect of the paper.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2023.07.002.

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