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Development of Focal Nodular Hyperplasia Post Dual Anti-HER2 Blockade with Pertuzumab and Trastuzumab in a Patient with Breast Cancer: A Case Report and Literature Review

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Abstract

Targeted therapies like trastuzumab and pertuzumab have substantially improved outcomes in HER2-positive breast cancer with rare reports of significant adverse events. One such rarely reported adverse event is focal nodular hyperplasia (FNH), an uncommon hepatic condition, typically benign and asymptomatic, but its development following dual anti-HER2 therapy is not commonly documented. We report the case of a 61-year-old woman with HER2-positive breast cancer highlighting the unusual development of FNH following dual anti-HER2 therapy. Routine follow-up imaging posttreatment revealed the development of hepatic nodules. Imaging confirmed a diagnosis of FNH, with no radiologic evidence of malignancy or metastatic disease. The patient remained asymptomatic, and following hepatology consultation, continuation of treatment was recommended with regular imaging follow-up to monitor hepatic lesions. Although it is benign and asymptomatic, FNH warrants careful monitoring in patients on prolonged targeted therapy. Further research is required to elucidate the mechanisms underlying the association between HER2-targeted therapies and hepatic alterations, which could inform evidence-based strategies for monitoring and management in clinical practice.

Keywords
- breast cancer
- dual anti-HER2 blockade
- focal nodular hyperplasia
- pertuzumab
- trastuzumab

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Introduction

HER2 overexpression is present in approximately 25% of breast cancers, often resulting in a more aggressive disease compared with breast cancers without HER2 overexpression. Targeted therapies such as trastuzumab and pertuzumab have greatly enhanced outcomes for patients with HER2-positive breast cancer.[1] These therapies are generally associated with fewer side effects. Hepatic complications are infrequently reported following the use of these anti-HER2 monoclonal antibodies.[2,3] This case report discusses a patient who developed focal nodular hyperplasia (FNH) of the liver after receiving trastuzumab and pertuzumab, highlighting the importance of considering potential hepatic toxicities in those undergoing dual anti-HER2 therapy.

Case Report

A 61-year-old postmenopausal woman with a medical history of hypertension, diabetes mellitus, and hypothyroidism presented with a left breast lump in May 2018. A core biopsy confirmed the diagnosis of breast cancer, immunohistochemistry showing positive estrogen receptor (ER), positive progesterone receptor (PR), and HER2 neu overexpression (3 +). She underwent a left modified radical mastectomy. Owing to the strong hormone receptor positivity and localized stage II disease, chemotherapy with targeted therapy was advised. However, the patient declined and was subsequently initiated on adjuvant anastrozole, an aromatase inhibitor.

The patient initially tolerated the adjuvant treatment well. However, 6 months into therapy, she began to experience bone pains and serous discharge from the anterior hip region. A positron emission tomography and computed tomography (PET-CT) scan in June 2019 showed no residual breast disease, but revealed mediastinal and abdominal lymphadenopathy with low-grade metabolic activity, along with an osteolytic lesion at the left anterior superior iliac spine with sinus tract formation. These findings indicated the presence of metastatic disease. The patient's treatment was transitioned to ribociclib, a CDK4/6 inhibitor, in combination with fulvestrant. Despite this change, a follow-up PET scan 3 months later showed no substantial reduction in the disease. With this history, the patient approached us for the next line of therapy. Consequently, the treatment regimen was changed to systemic chemotherapy with weekly Nab-paclitaxel (100 mg/m^2) and trastuzumab (4 mg/kg followed by 2 mg/kg), along with bone-modifying agent denosumab every 3 months. The patient tolerated 18 cycles of weekly chemotherapy achieving a remarkable response. Subsequent evaluations, including comprehensive liver function tests (LFTs) and an abdominal scan, demonstrated no evidence of liver disease. As a result, she was placed on maintenance therapy with trastuzumab and pertuzumab alongside fulvestrant starting from March 2020. The interim evaluations and PET scan in January 2024 confirmed the absence of active disease or any recurrence during this period, leading to the continuation of trastuzumab and pertuzumab with fulvestrant to date.

In July 2024, a follow-up PET-CT scan revealed an ill-defined hypodense lesion with clustered hypodensities in the splenic parenchyma, demonstrating increased metabolic activity (SUVmax of 8.7; ►**Fig. 1**), suggestive of a granulomatous pathology. Subsequent magnetic resonance imaging (MRI) of the abdomen showed an enhancing, geographic, non-mass-like lesion with indistinct margins in the spleen, which was not clearly visible on structural imaging, indicating a likely inflammatory or immune response rather than metastatic disease. Additionally, the MRI identified numerous (>20 lesions) arterial-enhancing nodular lesions (3–10 mm) with restricted diffusivity scattered throughout both liver lobes, which were not metabolically active (►**Fig. 2**). These findings were consistent with asymptomatic FNH or nodular regenerative hyperplasia. At the time of

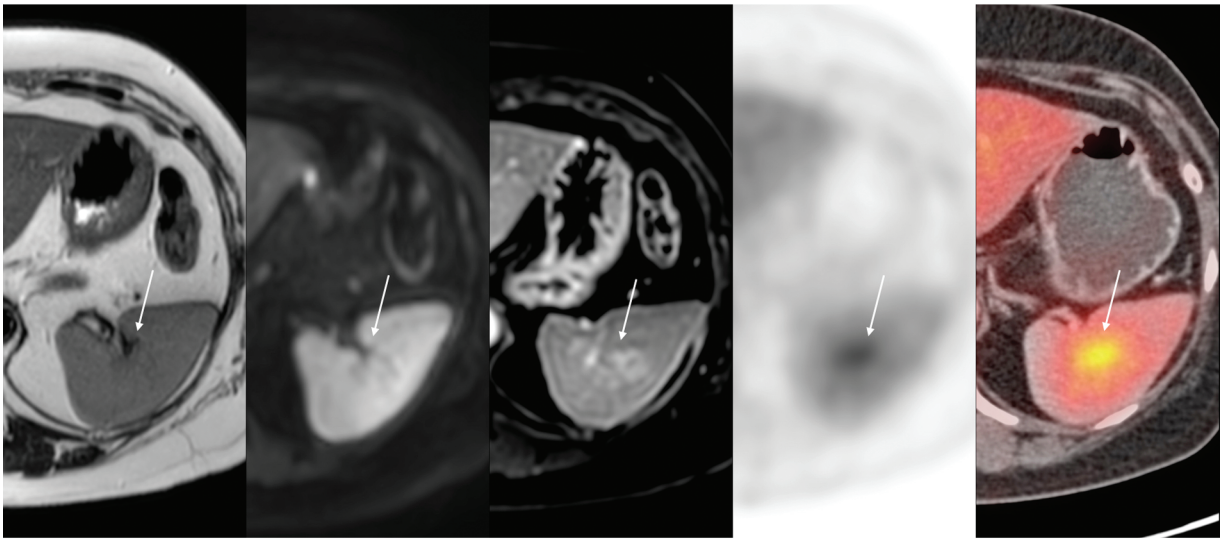

Fig. 1 Focal fluorodeoxyglucose (FDG) uptake adjacent the splenic hilum with mild enhancement without any signal alteration on T2-weighted/diffusion-weighted (DW) images.

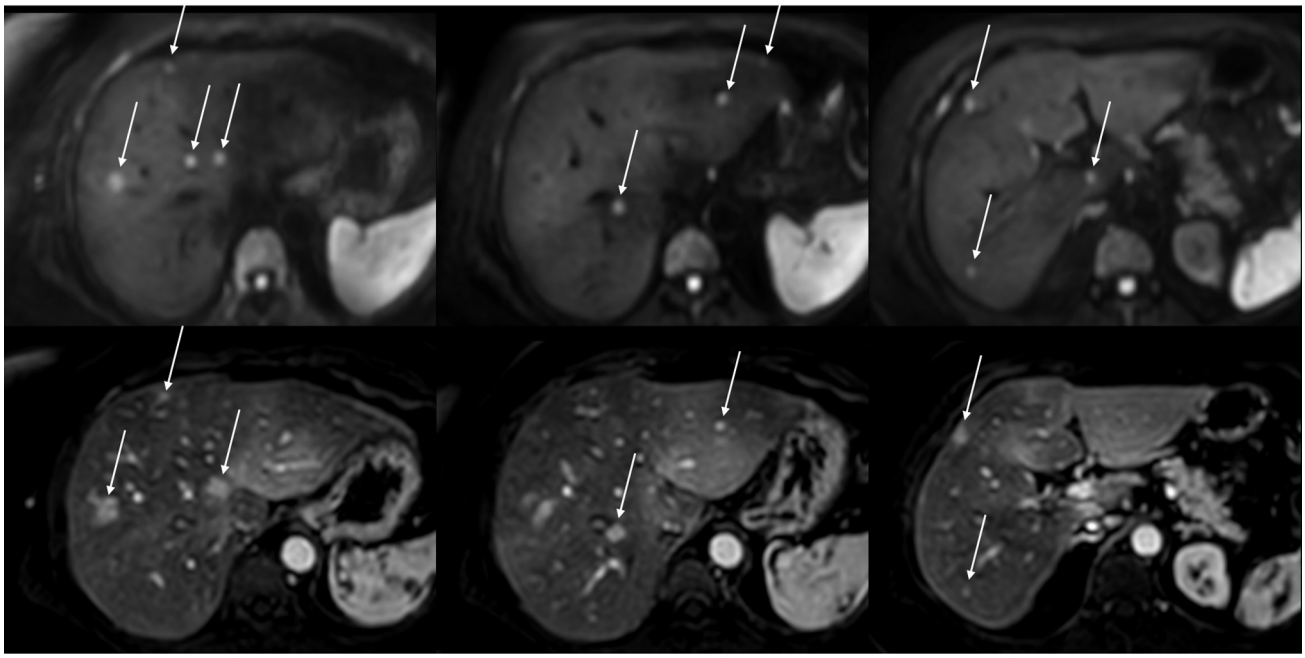

Fig. 2 Multifocal arterial enhancing lesions with diffusion-weighted (DW) hyperintensity scattered in both lobes of the liver.

hepatic nodule diagnosis, the patient's LFTs and tumor markers including alpha-fetoprotein (AFP) were within normal ranges, and viral hepatitis serology was negative. She also had no history of smoking, alcohol use, hepatotoxic medication use, or any relevant family history. Due to the patient's refusal of a liver biopsy, the absence of washout on MRI and lack of fluorodeoxyglucose (FDG) uptake on imaging led to the conclusion of FNH induced by trastuzumab and pertuzumab treatment. Hepatology consultation was taken and they advised the patient to continue trastuzumab + pertuzumab therapy and to observe the hepatic and splenic lesions over the next 3 to 6 months.

Discussion

This case highlights the development of FNH induced by administration of dual targeted therapy and the absence of history of chronic liver disease, smoking, alcohol, or medication use strongly suggests a cause–effect association.

FNH is marked by micronodularity (<0.2 cm) and diffuse transformation of the liver parenchyma without fibrosis, arising from altered intrahepatic blood flow. This causes reduced portal flow and hepatocyte atrophy, which is compensated by increased blood flow in adjacent areas, leading to hepatocyte hyperplasia and regenerative nodule formation.[4] Drug-induced FNH is rare and asymptomatic, typically arising after prolonged treatment and is most commonly associated with thiopurines, antiretrovirals, and platinum-based drugs.[5] Since most drug-induced FNH cases are asymptomatic and are without carcinomatous change, accurate diagnosis of hepatic nodules during therapy is crucial, as FNH and liver metastases have markedly different prognosis. MRI is currently considered the best noninvasive method for diagnosing drug-induced FNH, with a sensitivity of 70% and specificity of 98%.[6] A definitive diagnosis of classical FNH is easily made when MRI shows a homogeneous tumor with a central scar and arterial-phase hypervascular enhancement. In the present case, FNH was diagnosed using a combination of imaging techniques, including ultrasonography, PET-CT, and MRI, which have a reported diagnostic accuracy of up to 90%.[7]

Although there are limited data of anti-HER2 therapy causing FNH, cases of trastuzumab and pertuzumab directly causing liver hyperplasia have been reported. A case has been reported by Force et al wherein trastuzumab emtansine combined with pertuzumab was associated with the development of FNH of the liver.[8] In a clinical trial, a patient developed acute liver failure after receiving pertuzumab, trastuzumab, and docetaxel, although the role of pertuzumab in this event is unclear.[3] Liver injury linked to trastuzumab is typically self-limiting and not accompanied by symptoms like jaundice. In contrast, hepatotoxicity associated with ado-trastuzumab emtansine can often be severe and fatal.[9] Fulvestrant can cause liver enzyme elevation in up to 15% of cases, with rare instances of hepatitis and liver failure, but is not linked to steatosis or fatty liver disease.[10] Ribociclib, a CDK4/6 inhibitor, is primarily associated with neutropenia, QTc prolongation, and diarrhea, although rare cases of hepatotoxicity and pseudocirrhosis have been reported.

Hepatic changes typically appear after a median of two chemotherapy lines and four systemic treatments, including endocrine therapy and CDK4/6 inhibitors.[11] Trastuzumab inhibits HER2 signaling by binding to its extracellular domain, while pertuzumab complements this action by blocking HER2 heterodimerization and enhancing antibody-dependent cytotoxicity; both agents generally cause mild, transient liver enzyme elevations, with rare severe hepatotoxicity, particularly in combination therapies.[12] In present

case, the patient was asymptomatic and it was only an accidental finding and had no liver metastases, unlike most cases of history with liver cirrhosis that arises on preexisting liver metastases or after multiple lines of systemic therapy. Typical FNH is diagnosed through imaging without biopsy, and recognizing its imaging characteristics and related conditions enables accurate diagnosis, avoiding unnecessary anxiety and biopsy risks.[13] In the present case, MR images showing the absence of washout, along with PET scans indicating no FDG avidity, led to the diagnosis of FNH associated with trastuzumab and pertuzumab treatment.

To the best of our knowledge, the occurrence of FNH associated with the use of pertuzumab and trastuzumab is not well documented in the literature. The potential therapeutic approaches include withholding the treatment and reassessment or a change in therapy regimen. While FNH is generally considered benign and asymptomatic, its occurrence following targeted HER2 therapy warrants attention. The pathophysiological mechanisms linking dual anti-HER2 therapy, specifically trastuzumab and pertuzumab, to the development of FNH are not yet fully understood, but may involve vascular changes induced by the treatment. Further research is needed to clarify the relationship between anti-HER2 therapy with pertuzumab and trastuzumab and hepatic changes, and to establish evidence-based guidelines for monitoring and managing these conditions. Additionally, the absence of long-term follow-up data restricts the understanding of the potential progression of FNH in patients undergoing extended anti-HER2 therapy. Larger, prospective studies will help understand the incidence, risk factors, and clinical implications of FNH in this patient population.

Conclusion

Our experience suggests that FNH may develop as a rare side effect of dual anti-HER2 therapy with pertuzumab and trastuzumab. Although generally benign, this finding highlights the need for careful monitoring and further research to elucidate the relationship between these therapies and hepatic changes.

Patient Consent

Consent has been obtained from the patients.

Authors' Contributions

U.M., V.M. contributed to the intellectual content and manuscript review. R.D., N.S., B.J., K.G. contributed to the literature search and radiological intervention of the data. N.S. contributed to the data acquisition. R.D. contributed to the clinical studies. D.M. contributed to the manuscript preparation and medical writing.

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Conflict of Interest

None declared.

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