Annals of Clinical Case Reports

Case Report
Published: 05 Dec, 2022

# Pseudo-Cirrhosis of the Liver from Breast Cancer: A Case Report

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## Abstract

Breast cancer accounts for 43% of all solid tumors in women. Despite continuous improvement in therapy, breast cancer represents the main cause of cancer death in women. Notwithstanding the notable increase in the early diagnoses made possible by the spread of screening tests, still, 5% of breast malignancies show up as metastatic '*de novo*'. We report the case of a 56-years-old woman who, under a first-line therapy with Ribociclib and Fulvestrant developed pseudocirrhosis of the liver, i.e., liver cirrhosis due to the malignancy, but unrelated to the presence of liver metastases. This condition is a rare and poorly known clinical entity. There is no consensus on the criteria needed for diagnosis. Pathogenic mechanisms underlying etiology may be chemotherapy's toxicity or architectural changes in response to neoplastic micro-infiltration. However, an increase in transaminases and liver dysfunction are described with CDK 4/6 inhibitors therapy, probably due to direct drug-induced hepatotoxicity, immune-mediated activity, and production of toxic metabolites. Early hepatic alterations and/or radiological evidence of liver cirrhosis in the absence of neoplastic liver involvement, should suggest the diagnosis of such a rare condition.

## Introduction

About 6% of newly diagnosed breast cancer patients present at initial diagnosis with "*de novo*" metastatic disease [1]. The most common sites of distant metastases are bones (85%), liver (50%), lungs (25%), and brain (16%). According to statistics updated to 2022, the 5-year survival rate for mBC is 29%, but tumor histotypes affect survival outcome: indeed, women with TNBC and HER2-overexpressing tumors have a worse prognosis as compared to patients with Luminal one neoplasms [2]. Currently, CDK4/6 inhibitors have changed the natural history of Hormone Receptor-positive (HR+), HER2-negative, mBC. Indeed, from 2015 to 2017, Palbociclib, Ribociclib and Abemaciclib, in association with hormonal therapy, have been approved in both aromatase inhibitors-sensitive and – resistant HR+, HER2-negative mBC, based on the benefit in median Overall Survival (mOS) and median Progression Free Survival (mPFS) evidenced by the randomized phase III PALOMA, MONALEESA, and MONARCH trials, respectively [3,4].

CDK 4/6 inhibitors, which are widely used in clinical practice, differ in their safety profiles: neutropenia, QTc prolongation, diarrhea being often observed although at different rates [5]. Hepatotoxicity associated with CDK 4/6 inhibitors is an uncommon occurrence, characterized by an increase in AST and ALT (G3-G4) due to direct drug-induced, immune-mediated activity, and production of toxic metabolites. Moreover, in literature few cases of CDK 4/6 inhibitors-pseudocirrhosis are described. Pseudocirrhosis is defined by radiological features as in the case of true cirrhosis, appearing in patients without a history of heavy alcohol use, hepatitis B, hepatitis C, or pre-existing chronic liver disease; this condition predominantly affects patients with liver metastases who have previously received multiple chemotherapy regimens. The outcome is often worsened by portal hypertension and hepatocellular failure [6]. To our knowledge, this condition is a rare entity, most commonly observed in breast cancer patients. The absence of diagnostic criteria and the lack of data in the literature, make this unlike condition difficult to diagnose and, consequently, also to manage. Herein, we report an atypical presentation of pseudocirrhosis with peculiar radiologic features in a breast cancer patient, with progressive liver failure.

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**Received Date**: *14 Nov 2022*
**Accepted Date:** *29 Nov 2022*
**Published Date:** *05 Dec 2022*

***Citation:***
*D'Addario C, Sergi MC, Biasi A, Scardapane A, Gatti P, Stucci LS. Pseudo-Cirrhosis of the Liver from Breast Cancer: A Case Report. Ann Clin Case Rep. 2022; 7: 2359.*
***ISSN: 2474-1655.***

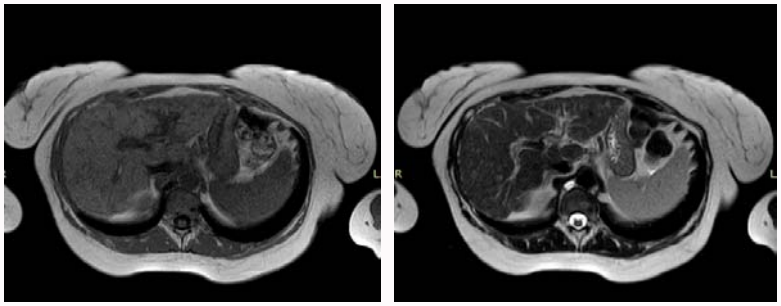

**Figure 1**: MR abdomen performed in August 2021, showed nodules of 2 mm to 16 mm in 5-6-7 liver segments with hypervascular rim.

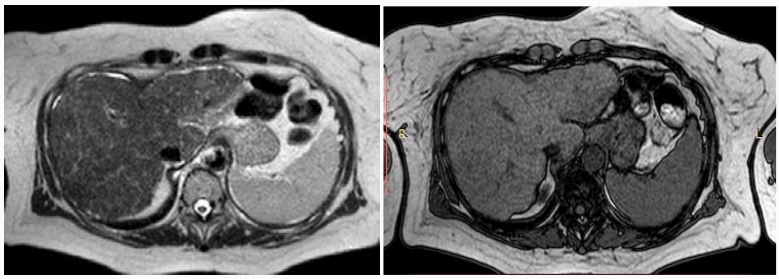

**Figure 2**: MR abdomen performed in November 2021, showed cirrhotic liver with micronodular pattern, not focal lesions.

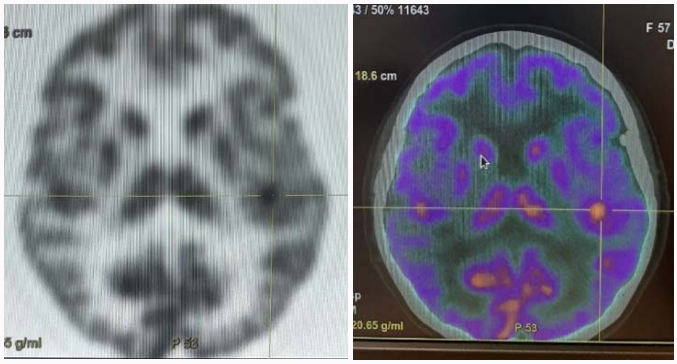


**Figure 3**: PET scan performed in February 2022, showed hyperaccumulation of the radiopharmaceutical in brain's left temporal lobe ($SUV_{max}$ 16.5).

## Case Presentation

A 53-years-old female patient was referred to our center in November 2017 for a histological diagnosis of breast cancer. She has undergone a right breast quadrantectomy in October 2017 for a ductal mammary carcinoma staged as pT1bN2a (st. IIIa), G2, Luminal A. Sequencing analysis of the BRCA2 gene by Next Generating Sequencing (NGS) revealed the presence of a pathogenetic variant of the gene. After excluding distant metastasis, the patient received 4 cycles of Epirubicin plus Cyclophosphamide followed by 12 cycles of Paclitaxel as adjuvant chemotherapy. After chemotherapy, she started hormonotherapy with Letrozole. In March 2021, during follow-up, an abdominal Computed Tomography (CT) showed a vertebral lesion, confirmed by bone scintigraphy with additional evidence of multiple lesions affecting all bone segments examined. A total body CT scan identified no further distant metastases. Therefore, in May 2021, she started a first-line therapy with Ribociclib plus Fulvestrant, together with an anti-resorptive therapy with Zoledronic Acid. In August 2021 owing to the elevation of transaminases (AST 97 UI/l, ALT 67 UI/l), an abdominal Magnetic Resonance Imaging (MRI) showed the presence of hepatic nodules (more likely cystic) of the size of 12 mm to 16 mm, in the segments V, VI and VII (Figure 1). In November 2021, a control abdominal MRI evidenced a dysmorphic, irregular, and micronodular hepatic pattern, suggestive of liver cirrhosis (Figure 2). Hepatitis virus infection tests and autoimmune hepatitis markers were negative. The patient denied alcohol abuse. An increase in CA15.3 levels was also documented (93 U/ml) (Table 1). Hence, the patient underwent liver biopsy, which evidenced a micro-infiltration of breast cancer in the liver parenchyma, the neoplastic population being GATA 3+, CK 19+, E-caderin+/-, ER <1%, PgR <1%, Hepatoyte-, Ki-67 7%, Her2 score 0). A disease progression was thus diagnosed. She refused chemotherapy, and thus Talazoparib monotherapy was administered as second-line therapy, due to the presence of the BRCA 1/2 mutation. In February 2022, a PET scan found unexpectedly no liver uptake, but a lesion in the brain's temporal lobe (SUVmax 16.5) was documented (Figure 3). A total-body CT confirmed a stable disease. Lab tests showed a worsening of liver function, with hyperbilirubinemia, hypoalbuminemia, and hyperammonemia (Table 2 and Figure 4). She exhibited signs of ascites and progressive clinical and cognitive deterioration. Talazoparib treatment was stopped, and we referred her to the best supportive care unit.

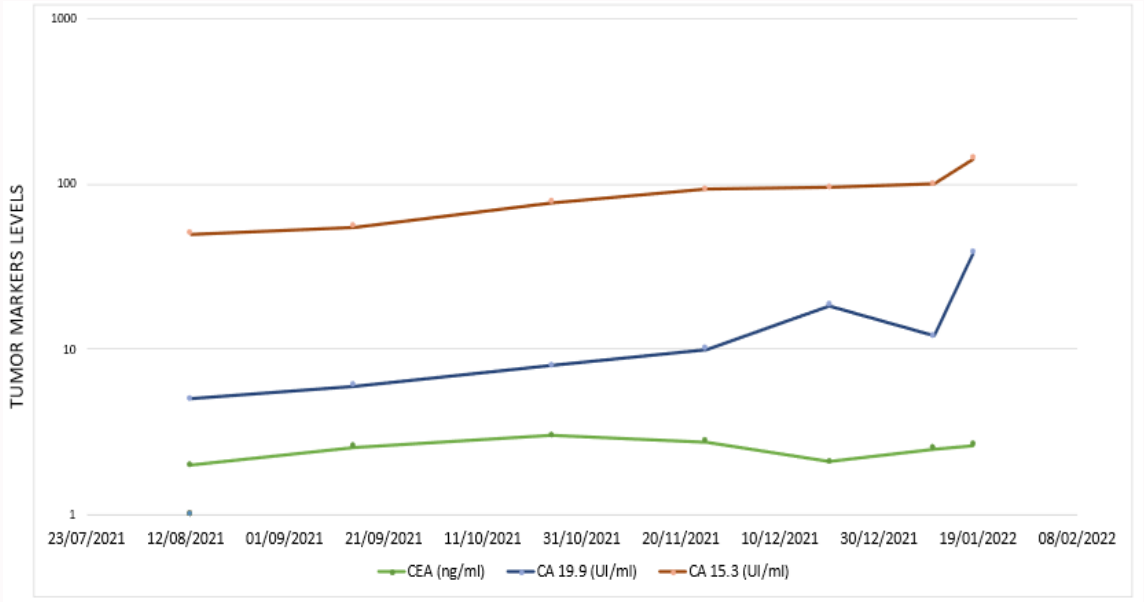


**Figure 4**: Lab tests showed a worsening of liver function, with hyperbilirubinemia, hypoalbuminemia, and hyperammonemia.

**Table 1**: Progress of tumor markers.

| Lab Tests | 15-09-2021 | 10-11-2021 | 18-01-2022 |
|---|---|---|---|
| CEA ng/ml (0-3) | 2.56 | 2.76 | 2.65 |
| Ca 19.9 UI/mL (0-40) | 5 | 7.7 | 38.5 |
| Ca 15.3 UI/mL (0-32.4) | 74.2 | 93 | 142.8 |

**Table 2**: Progress of lab tests and Child-Pugh score.

| Lab Tests | 20-12-2021 | 04-02-2022 | 22-02-2022 |
|---|---|---|---|
| Bilirubin | 1.2 mg/dl | 1.46 mg/dl | 4.60 mg/dl |
| Albumin | 3.66 g/d | 3.40 g/d | 3.00 g/d |
| INR | 1.04 | 1.22 | 1.26 |
| Ascites | No | Yes | Yes |
| Encephalopathy | No | No | No |
| Child-Pugh score | A | B7 | C 12 |

## Discussion

Liver cirrhosis from cancer also called pseudocirrhosis, is a rare and poorly understood clinical entity, most common in breast cancer patients. Pseudocirrhosis is characterized by architectural changes resulting in the reduction of liver volume, development of irregular and dysmorphic nodularity, and fibrotic retraction. In contrast to true cirrhosis, fibrotic bridges between nodules are absent and clinical status rapidly declines caused by hepatic failure complications (ascites, splenomegaly, and varices). Pathogenicity factors associated with liver disease involve changes induced by the micro-infiltration of the tumor and toxicity linked to systemic therapy. The liver is one of the most common sites of breast cancer spread, thus in liver metastases of chemotherapy-naïve patients, a desmoplastic reaction surrounding the tumor may lead to hepatic impairment. On the other hand, necrosis induced by chemotherapy likely causes nodular regenerative hyperplasia with sinusoidal obstruction syndrome, a process underlying vascular injury and long-term fibrosis. Moreover, the response of liver metastases to chemotherapy exacerbates scarring and fibrotic retraction [6]. Most cases of pseudocirrhosis described in the literature, are thus related to chemotherapy. Dan Engelman et al. [7] suggested that hepatic alterations arise after a median of 2 lines of chemotherapy and after a median of 4 lines of systemic treatments for metastatic disease (endocrine therapy, CDK 4/6 inhibitors or chemotherapy). Particularly, this condition occurs mainly during treatment with 5-FU, cisplatin, and a combination of 5-FU and cisplatin in advanced stages. Therefore, careful anamnesis, blood tests for hepatitis virus infection, and markers of autoimmune hepatitis are needed to exclude other possible causes of cirrhosis. When the first abnormalities of the hepatic parenchyma emerge from the diagnostic imaging, the liver function is preserved, delaying the diagnosis of pseudocirrhosis. Signs of liver failure such as hypoalbuminemia, hyperbilirubinemia, and coagulation disorders may arise in more advanced stages with the onset of hepatic failure; this dramatic condition, of course, must be differentiated from hepatic failure from cancer progression in the liver. Furthermore, in advanced cancer patients, malnutrition represents a confounding factor, because of altered levels of albuminemia in the blood [6]. The lack of valid data in the literature makes it difficult to manage these patients: Potential therapeutic approaches include supportive care, steroid treatment, and a change in systemic therapy [8]. In our case, at the time of presentation, our patient had completed adjuvant chemotherapy and had no liver metastases, unlike most cases of liver cirrhosis that arises on pre-existing liver metastases or after multiple lines of systemic therapy. Liver disease onset is very unusual with unexpected evolution. Hepatic neoplastic micro-infiltration reported in MR images revealed an atypical liver involvement. In addition, PET showed no hepatic uptake, but FDG avidity in brain's temporal lobe with no morphological abnormality on corresponding CT images. We supposed that bilirubin elevation triggered hepatic encephalopathy, causing hypermetabolism in the area of the limbic system, as reported in some case series [9]. Furthermore, she experienced liver cirrhosis during Ribociclib plus Fulvestrant therapy, only sporadic cases of hepatotoxicity related to CDK 4-6 inhibitors having been described in the literature to date. To our knowledge, Ribociclib is most frequently associated with liver-related adverse events compared to the other two agents (Palbociclib and Abemaciclib), due to the suppression of hepatic transporters and direct drug-induced hepatotoxicity, resulting in the

production of toxic metabolites. In the MONALEESA-3 trial, which investigated Ribociclib plus Fulvestrant for postmenopausal women after progression on endocrine therapy, Grade 3 or 4 hepatobiliary adverse events occurred in 13.9% of patients who received Ribociclib, but none of these cases resulted in death or hepatic impairment [4,8]. Despite the discontinuation of CDK 4/6 inhibitors therapy, liver tests did not normalize. The patient was considered to have progressive disease after liver biopsy. She refused chemotherapy; thus, we chose Talazoparib therapy based on the results of EMBRACA trial. Unfortunately, our patient died few weeks after starting Talazoparib, 8.5 months since the initial diagnosis of pseudocirrhosis. This data reflects the findings of a small retrospective observational study of patients with liver cirrhosis from breast cancer, where the mOS from diagnosis of pseudocirrhosis was 10.0 months [6]. Despite chemotherapy is the best choice to prevent severe organ dysfunction referred to as visceral crisis, the gold standard therapeutic strategy for pseudocirrhosis remains an unmet need due to limited available data and the aggressive behavior of the disease.

## Conclusion

Liver cirrhosis from breast cancer is a condition rarely found in these patients, usually diagnosed at an advanced stage, and characterized by a poor prognosis. Prospective data are lacking and this, together with the absence of specific diagnostic criteria and to provenly active therapeutic interventions, makes this condition difficult to identify and treat. Early recognition of the disease and its complications (such as hepatic encephalopathy) could prevent rapid progression to liver failure and increased morbidity. Unfortunately, due to poor performance status and liver dysfunction, the best supportive care is often the only viable way. Early hepatic alterations and/or radiological evidence of liver cirrhosis in the absence of neoplastic liver involvement, should suggest the diagnosis of such a rare condition.

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