



Pseudocirrhosis in Patients with Metastatic Breast Cancer after Treatment with Eribulin

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Abstract

Pseudocirrhosis, an important complication of metastatic disease, is rarely seen and most commonly described in patients with breast cancer. Despite its radiological and clinical similarity with cirrhosis, it is different pathophysiologically. Eribulin, a novel synthetic chemotherapeutic agent, is one of the few choices of treatments that prolong overall survival in metastatic breast cancer who previously treated with multiple chemotherapy regimens. Herein we report two patients with breast cancer and liver metastasis who developed pseudocirrhosis after achieving a clinical and radiographic response to eribulin.

Keywords: Breast cancer; Pseudocirrhosis; Eribulin

Introduction

Breast cancer is the most common malignant disease diagnosed in women and affects one in eight women over a lifetime in the world. At the time of diagnosis approximately 40% of women presented with invasive breast cancer have regional spread or distant metastases and during the course of the disease about half of metastatic breast cancer patients have metastasis to the liver. Treatment of these patients presents a difficult clinical problem with the involvement of the liver [1]. Because of several commonly used cytotoxic drugs in the treatment of advanced breast cancer are activated or metabolized by the liver, administration of chemotherapy can be complicated [2]. Systemic chemotherapy has well known hepatotoxic effects which are increase serum levels of hepatic enzymes, fatty infiltration of the liver, focal hepatitis, portal fibrosis, pseudocirrhosis, and hepatic necrosis [3]. Pseudocirrhosis radiographically like macronodular cirrhosis and can cause hepatic decompensation, whereas histopathologically cirrhosis is absent. Liver metastatic breast cancer treated with chemotherapy is the most prominent cause of pseudocirrhosis [4].

Eribulin, a novel synthetic chemotherapeutic agent, is microtubule inhibitor differs from Taxanes by the site of action. Eribulin is one of the few choices of treatments that prolong overall survival in metastatic breast cancer who previously treated with multiple chemotherapy regimens [5]. We report two patients with breast cancer and liver metastasis who developed pseudocirrhosis after achieving a clinical and radiographic response to eribulin.

Case Presentation

Case 1

A 56-year-old female patient was diagnosed with invasive ductal adenocarcinoma of the left breast in the locally advanced stage. After surgery, adjuvant chemotherapy with FEC (5-Fluorouracil, Epirubicin, Cyclophosphamide) and Docetaxel was administered followed by locoregional radiotherapy and Letrozole. After 19 months, multiple metastatic hepatic lesions were detected. The patient was treated by weekly Paclitaxel, Gemcitabine, Docetaxel and Capecitabine in order. After this treatment progression was observed and eribulin was initiated. Before eribulin treatment laboratory findings were: hemoglobin: 13.2 g/dL; leukocyte count: 4.850 mm³; platelet count: 298.400 mm³; albumin: 3.4 g/dL; total protein: 6.95 g/dL; Aspartate Aminotransferase (AST): 165 U/L; Aminotransferase (ALT): 99 U/L; Alkaline Phosphatase (ALP): 142 U/L; Gamma-Glutamyl Transpeptidase (GGT): 846 U/L; Lactate Dehydrogenase (LDH): 278U/L; total bilirubin: 1.72 mg/dL. Hepatitis B and C viral infection markers were negative. As tumor markers Carcinoembryonic Antigen (CEA) was 5.4 ng/mL and serum Carbohydrate Associated Antigen (CA) 15-3 was 616 U/mL (normal range <25 U/mL). F18-Fluorodeoxyglucose Positron emission tomography (18F-FDG PET-CT) showed bone metastases and bilobar liver lesions with SUV_{max} value (standardized uptake

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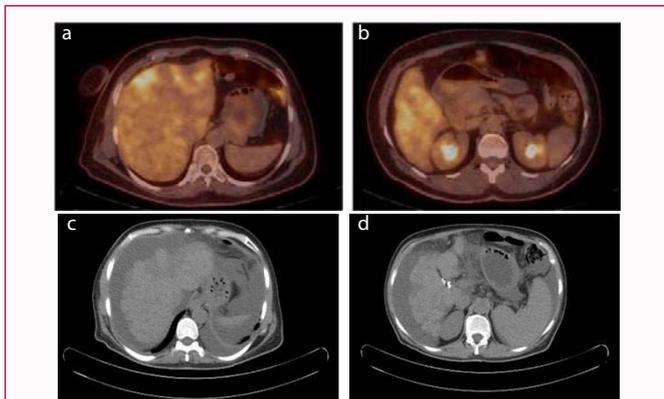


Figure 1: F18 FDG PET CT axial and fusion images (A,B) show increased activity in bilobar hepatic metastases before eribulin treatment. After 6 cycles of eribulin CT scan (C,D) shows regression in metastatic lesions, decreased hepatic volume, irregular contours consistent with pseudocirrhosis and newly developed ascites as the sign of portal hypertension.

value) 5,7 which has hypometabolic center because of necrosis (Figure 1A and 1B). A follow-up 18F-FDG PET CT performed after 6 cycles of eribulin showed the development of decreased hepatic volume, irregular contours, heterogeneously increased activity, regression in metastatic lesions and newly developed ascites (Figure 1C and 1D). After eribulin treatment laboratory findings were: hemoglobin: 10.2 g/dL; leukocyte count: 3.540 mm³; platelet count: 92.860 mm³; albumin: 2.6 g/dL; total protein: 6.9 g/dL; AST: 29 U/L; ALT: 13 U/L; ALP: 72 U/L; GGT: 78 U/L; LDH: 206 U/L; total bilirubin: 0.7 mg/dL; International Normalized Ratio (INR): 1.09. CA15-3 had decreased to 52.95 U/mL. Serum-ascites albumin gradient was calculated as 1.7. Ascites cytology was evaluated as benign. She could not continue treatment with eribulin later due to toxicity. The other agents were inappropriate because of performance status. The patient died after 24 months of liver metastasis due to hepatic failure caused by metastasis.

Case 2

A 47-year-old female patient was consulted for left breast mass which was diagnosed as invasive ductal adenocarcinoma by biopsy. Liver metastasis was detected with imaging. Doxorubicin with Cyclophosphamide subsequently Docetaxel with Trastuzumab treatments were given to the patient for palliative treatment. Follow-up Computerized Tomography (CT) scan performed after chemotherapy showed complete regression of the liver metastasis. Then she underwent mastectomy and radiation therapy was applied followingly. Trastuzumab treatment completed to one year. During follow-up, recurrence with multiple liver and newly bone metastases was detected. The patient was treated in-orderly by Lapatinib with Capecitabine, Navelbin with Trastuzumab, Paclitaxel with Carboplatin and one agent Gemcitabine for palliation. After this treatment progression was observed in the liver and bone a lesion by CT scan and eribulin therapy was started (Figure 2A). Before eribulin treatment laboratory findings were: hemoglobin: 9 g/dL; leukocyte count: 15.370 mm³; platelet count: 123.000 mm³; albumin: 2.7 g/dL; total protein: 6.4 g/dL; AST: 54 U/L; ALT: 40 U/L; ALP: 388 U/L; GGT: 722 U/L; LDH: 253 U/L; total bilirubin: 1.49 mg/dL. Hepatitis B and C viral infection markers were negative. As tumor markers Carcinoembryonic Antigen (CEA) was 16 ng/mL (normal range <5 ng/mL) and serum Carbohydrate Associated Antigen (CA) 15-3 was 48 U/mL (normal range <25 U/mL). CT scan performed after 8 months of eribulin treatment showed regression of liver metastases, liver parenchyma heterogeneity, lobular appearance, capsule retraction and splenomegaly (Figure 2B). After eribulin treatment laboratory findings were: hemoglobin: 12 g/dL; leukocyte count: 4.220 mm³; platelet count: 72.890 mm³; albumin: 2.4 g/dL; total protein: 5 g/dL; AST: 37 U/L; ALT: 30 U/L; ALP: 245 U/L; GGT: 390 U/L; LDH: 252 U/L; total bilirubin: 0.57 mg/dL; INR: 0.93. CA15-3 had decreased to 26 U/mL and CEA had decreased to 0.78 ng/mL. On the 22nd month of treatment with eribulin progression was observed and treatment was continued with Trastuzumab emtansin. After 3 cycles patient died of hepatic failure caused by metastasis.

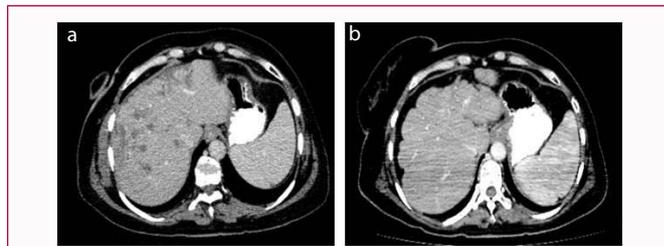


Figure 2: Contrast-enhanced CT axial image (A) before eribulin treatment shows multiple liver metastases. After 8 months of eribulin CT scan (B) shows regression in metastatic lesions, liver parenchyma heterogeneity, lobular appearance, capsule retraction consistent with pseudocirrhosis and splenomegaly as the sign of portal hypertension.

retraction and splenomegaly (Figure 2B). After eribulin treatment laboratory findings were: hemoglobin: 12 g/dL; leukocyte count: 4.220 mm³; platelet count: 72.890 mm³; albumin: 2.4 g/dL; total protein: 5 g/dL; AST: 37 U/L; ALT: 30 U/L; ALP: 245 U/L; GGT: 390 U/L; LDH: 252 U/L; total bilirubin: 0.57 mg/dL; INR: 0.93. CA15-3 had decreased to 26 U/mL and CEA had decreased to 0.78 ng/mL. On the 22nd month of treatment with eribulin progression was observed and treatment was continued with Trastuzumab emtansin. After 3 cycles patient died of hepatic failure caused by metastasis.

Discussion

Pseudocirrhosis, an important complication of metastatic disease, is rarely seen and most commonly described in patients with breast cancer [6]. Despite its radiological and clinical similarity with cirrhosis, it is different from cirrhosis pathophysiologically. It has got the same morphological changes as cirrhosis including parenchyma atrophy, nodularity, capsular retraction, and caudate lobe hypertrophy [7,8]. Chemotherapy administered liver metastatic breast cancer is the most commonly reported cause of pseudocirrhosis, but it can be associated with other metastatic diseases, including pancreatic cancer, colon cancer, medullary thyroid cancer and esophageal cancer [4,9-11].

Pseudocirrhosis occurred by multifactorial mechanism including; scarring and capsular retraction caused by chemotherapy as a result of treatment response, hepatic metastasis encircled by fibrous tissue, and chemotherapy-induced hepatic ischemia result in nodular regenerative hyperplasia. Another proposed mechanism is chemotherapy-induced sinusoidal obstruction [8,12,13].

While some patients diagnosed incidentally in an asymptomatic period on surveillance imaging, typically many patients present with portal hypertension complications such as ascites, portosystemic venous collaterals, and splenomegaly [13].

The exact prevalence of pseudocirrhosis is not known. In one retrospective study, all 22 liver metastatic breast cancer patients had pseudocirrhosis detected by abdominal CT scans whereas 52% and 27% of cases had ascites and splenomegaly, respectively [14].

Qayyum et al. reviewed data of 91 patients treated with chemotherapy for breast cancer with hepatic metastasis retrospectively. Hepatic contour abnormalities were detected in 75% of patients during 15 months median follow-up period. Sixteen of 68 patients developed diffuse nodularity resembling cirrhosis. Portal hypertension developed in 6 of 16 patients with diffuse nodularity and 1 of 42 patients with limited contraction [8]. In another study, 29(50%) of 58 patients with hepatic metastasis from breast cancer had various degrees of hepatic capsular retractions [15].

In our cases, CT scan showed capsule retraction and lobular appearance consisted with pseudocirrhosis related to treatment response which was disappearance of the liver lesion by CT and decrease level of tumor markers. In both cases, ascites and splenomegaly occurred as a complication of portal hypertension.

A wide range of chemotherapeutic agents like Adriamycin, Cyclophosphamide, 5-Fluorouracil, Methotrexate, Cisplatin, Gemcitabine, Tamoxifen, Paclitaxel, Capecitabine, Trastuzumab and Navelbine may cause pseudocirrhosis in patients with breast cancer [8,14,16].

To our knowledge, this represents the first reported case of pseudocirrhosis arising in the setting of regression of liver metastases from breast cancer treated with eribulin.

In conclusion, pseudocirrhosis can be diagnosed in tumor metastasis, progression, and chemotherapy responsive patients. Histopathologic evaluation of liver biopsy is crucial but it is invasive, on the other hand, most cases can be diagnosed by tumor markers and imaging methods like in our cases. It must be remembered that monitorization of hepatic decompensation and portal hypertension complications are as important as the cancer treatment.

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