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Clinical Profile and Prognosis of Metastatic Breast Cancer with Pseudocirrhosis: A Rare and Dismal Condition

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Abstract

Background: Pseudocirrhosis (PC) is an uncommon condition characterized by radiological abnormalities suggestive of cirrhosis in individuals with liver metastasis, particularly those with metastatic breast cancer (MBC). The prognosis is unfavorable, often leading to liver failure, emphasizing the need for a deeper understanding of the associated clinical and pathological factors.

Methodology: In this retrospective study, we examined patients with MBC who developed PC. The primary objectives were to delineate the clinical and pathological profiles of individuals with both PC and MBC and to assess overall survival (OS) based on various epidemiological, clinical, and pathological features.

Findings: The study included 44 patients, with a median age of 55.5 years. The luminal subtype was predominant in 83.3% of cases, and 54.6% exhibited metastases beyond the liver. The term "lobular contour" was commonly used in radiological descriptions of PC. The median time from the onset of liver metastasis to PC diagnosis was 33.3 months, and the median OS from PC diagnosis was 3.2 months. OS varied depending on histological type, number of metastases, prior chemotherapy lines, the cause of PC, and biochemical findings.

Conclusions: This study represents one of the most extensive series on PC in MBC. The median OS for PC patients was notably low and demonstrated variation based on the underlying cause of PC. Laboratory parameters, including aminotransferase, bilirubin, and albumin, may be useful as potential prognostic biomarkers

Keywords: Pseudocirrhosis; Metastatic breast cancer; Liver disease

Introduction

Pseudocirrhosis (PC) refers to radiological features indicative of hepatic cirrhosis in patients with cancer who have developed liver metastasis without prior evidence of liver disease. These alterations often present with clinical signs of liver failure, contributing to a extremely prognosis. The diagnosis relies on radiological evidences, showcasing morphological changes in liver contour, diffuse nodularity, capsular retraction, and parenchymal atrophy, mimicking chronic liver failure without histopathological confirmation of cirrhosis [1,2].

Metastatic breast cancer (MBC) is the most frequently associated tumor with PC. Luminal tumors, followed by HER2-positive tumors, are commonly

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reported in PC, though the pathological correlation between hormone-receptor-positive (HR+) breast cancer and PC remains unclear [3,4]. Other cancers, such as pancreatic, esophageal, gastric, lung, colorectal, and thyroid cancers, have also been linked to PC [5,6].

The pathophysiology of PC is complex and often multifaceted. PC may become evident as an initial presentation of liver metastasis or as a response to chemotherapy-induced hepatic injury, leading to scarring, capsular retraction, nodular regenerative hyperplasia, and sinusoidal obstruction syndrome [4,8]. While radiological findings in PC resemble cirrhosis, distinct biopsy patterns, such as regenerating nodules of hepatocytes and bridging fibrosis, differentiate the two entities [9,10].

In the context of MBC, commonly used chemotherapeutics are associated with PC, including doxorubicin, cyclophosphamide, methotrexate, 5-fluorouracil, cisplatin, vinorelbine, vincristine, oxaliplatin, capecitabine, and gemcitabine. Literature also describes associations of PC and trastuzumab, endocrine therapy (tamoxifen and megestrol), and multikinase inhibitors (regorafenib and sunitinib) [4,11].

Despite its rarity, PC is linked to a poor prognosis, high morbidityand mortality in MBC patients, with limited literature about the issue. This study aims to delineate the clinical and pathological profile of MBC patients developing PC and analyze their overall survival (OS) based on clinical, pathological, and laboratory variables.

Material and Methods

Study population

This study is both observational and retrospective, encompassing all patients diagnosed with PC and MBC who received treatment at A.C. Camargo Cancer Center, Brazil, between January 2010 and December 2020. Identification of patients involved an active search of computerized medical records utilizing keywords (pseudocirrhosis and chronic liver disease) and the selection of individuals with liver imaging characteristics suggestive of PC, determined through computed tomography (CT) or magnetic resonance imaging (MRI). Following an independent assessment by the radiology team, patients with MBC exhibiting CT scans or MRI images indicative of PC were included. Clinical, pathological, and laboratory data for this cohort were extracted from medical records. Exclusion criteria encompassed patients whose diagnosis did not align with MBC and/or lacked radiological evidence of liver cirrhosis. Individuals with pre-existing liver disease and primary liver cancer were also excluded.

Statistical analysis

Descriptive demographic characteristics were analyzed using frequencies, means, and medians. Group characteristic comparisons were conducted through an association analysis between categorical variables, employing the chi-square test or Fisher's exact test as appropriate. Survival analysis, disease control time, and the assessment of prognostic factors were estimated using the Kaplan-Meier method. Cox proportional-hazards models were employed to delineate factors associated with survival, though no multivariate analysis was conducted due to the limited sample size. Two-tailed p values <0.05 were considered statistically significant. The statistical analysis was carried out using SPSS software version 24.

Results

Clinical and pathological profiles of patients

In the cohort of 44 patients assessed, all were females diagnosed with MBC. The median age at the diagnosis of PC was 55 years. Ductal carcinoma emerged as the predominant histological type, accounting for 79.5% (n=35) of cases, followed by lobular carcinomas (6.8%; n=3) and mixed carcinomas (6.8%; n=3). Among the patients, 84.1% (n=37) were hormone receptor-positive (HR+), 11.4% (n=5) were HER2 positive, and 4.5% (n=2) had triple-negative breast cancer. (Table 1)

Table 1: Clinical and pathological characteristics of the patients.

Clinical and pathological findings (n=44)	Number of patients (%)
Histological type	
Ductal carcinoma	35 (79.5)
Lobular carcinoma	3 (6.9)
Mixed carcinoma	3 (6.9)
Molecular subtype	
Luminal	37 (84.1)
HER2 or luminal/HER2	5 (11.4)
Triple negative breast cancer	2 (4.5)
Number of metastasis	
≥ 2	23 (52.3)
0 or 1	21 (47.7)
Presence of ascites	22 (50)
Presence of esophageal varices	2 (10)
Previous lines of hormone therapy	
≥ 2	24 (57.1)
0 or 1	18 (42.8)
Previous lines of chemotherapy	
≥ 2	27 (64.2)
0 or 1	15 (35.7)

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The interval from the onset of metastatic disease to the manifestation of PC was 33.3 months. Notably, 52.5% (n=23) of patients exhibited metastases in two or more sites beyond the liver. Predominantly, bone was the most frequent metastatic site, identified in 84.1% of cases (n=37), followed by lung (27.3%; n=12), lymph nodes (22.7%; n=10), pleura (13.6%; n=6), and the central nervous system (13.6%; n=6). Ascites was present in 50% of cases (n=22), while information regarding esophageal varices was available for only 10% of the cases.

Laboratory findings

Considering valid data (N=36), 61.1% of patients exhibited aspartate aminotransferase (AST) levels ≥ 2 times the upper limit, and 27.8% had AST levels ≥ 5 times the upper limit. Alanine aminotransferase (ALT) levels were elevated in 29.1% of cases ≥ 2 times the upper limit. Approximately 44.4% of patients presented with elevated bilirubin (>1.1mg/dL), and 59.3% displayed a reduced albumin level (<3.5 g/dL). (Table 2)

Radiological characteristics

The majority of patients underwent evaluation through CT scans (95%). Predominant radiological terms used to characterize PC included lobular contour (76.7%), capsular retraction (32.6%), and heterogeneous attenuation (81.4%), as illustrated in figures 1 and 2. At the time of PC development, 88.4% exhibited multiple metastatic lesions, defined as five or more hepatic lesions.

Treatment received

Concerning prior lines of endocrine therapy, 40.9% (n=18) received up to 1 line, while 54.5% (n=24) received 2 or more lines. A majority of the population (61.4%; n=27) underwent at least 2 lines of chemotherapy before PC diagnosis. Common regimens included platinum, taxanes, or gemcitabine. At PC diagnosis, 38.6% experienced disease progression (PD), 27.3% had stable disease (SD), and 15.9% achieved partial response (PR). No complete responses (CR) were observed. Following PC onset, 70.5% (n=31) halted ongoing treatment, with 40.9% (n=18) transitioning to a new treatment strategy.

Long-Term survival outcomes

The median follow-up since the diagnosis of metastatic disease was 111 months, and since the diagnosis of PC, it was 18 months. The overall survival (OS) for metastatic disease was 50.4 months, and for PC, it was 3.2 months. Notably, 38.6% of the sample developed PC during disease progression, exhibiting a median OS of 2.2 months, compared to 15.4 months for those without progression (hazard ratio (HR) 2.4; 95% confidence interval (CI) 1.1 - 5.3; p=0.035). (Figure 1) PC occurred post-treatment response in 15.9% of cases, with this subgroup showing an OS of 15.7 months versus 2.2 months for non-responders (HR 2.6; 95% CI 1.0 - 6.2; p=0.029). (Figure 2) PC arising from treatment toxicity in 4.9% of patients did not exhibit a significant difference in OS compared to those without toxicity: 1.9 months versus 2.7 months, respectively.

Table 2: Biochemical findings and survival data.

Biochemical analysis	N (%)	OS (months)	HR	95% CI	p
AST level					
≥ 2 times the upper limit	22 (61.1)	2.2	2.9	1.2 -7.1	0.019
< 2 times the upper limit	14 (38.9)	15.2	1		
≥ 5 times the upper limit	10 (27.8)	0.9	5.3	2.1 - 13.0	< 0.001
< 5 times the upper limit	26 (72.2)	6.3	1		
ALT level					
≥ 2 times the upper limit	11 (29.7)	1.9	2.4	1.0 - 5.5	0.039
< 2 times the upper limit	26 (70.3)	3.9	1		
≥ 5 times the upper limit	3 (8.1)	6.9			
< 5 times the upper limit	34 (91.1)	3.2			
Bilirubin					
> 1.1mg/dL	16 (44.4)	1.8	4.2	1.8 - 9.7	0.001
0.2 - 1.1mg/dL	20 (55.6)	15.2	1		
Albumin					
< 3.5g/dL	14 (58.3)	1.2	5.1	1.8 - 14.6	0.003
3.5 - 5.2g/dL	10 (41.7)	15.2	1		

N: number; OS: overall survival; HR: hazard ratio; CI: confidence interval; AST: aspartate aminotransferase; ALT: alanine aminotransferase

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Examining OS by histological subtype, the HER2-positive group demonstrated an OS of 26.9 months, while the luminal subtype and triple-negative breast cancer exhibited OS values of 2.6 months and 0.03 months, respectively. For patients with two or more metastatic sites other than the liver, the OS was 3.2 months, compared to 2.3 months for those with up to one metastatic site, though statistical significance was not observed. Patients with hepatic and bone metastasis had an OS of 2.2 months, whereas those with visceral metastasis only had a survival of 3.2 months.

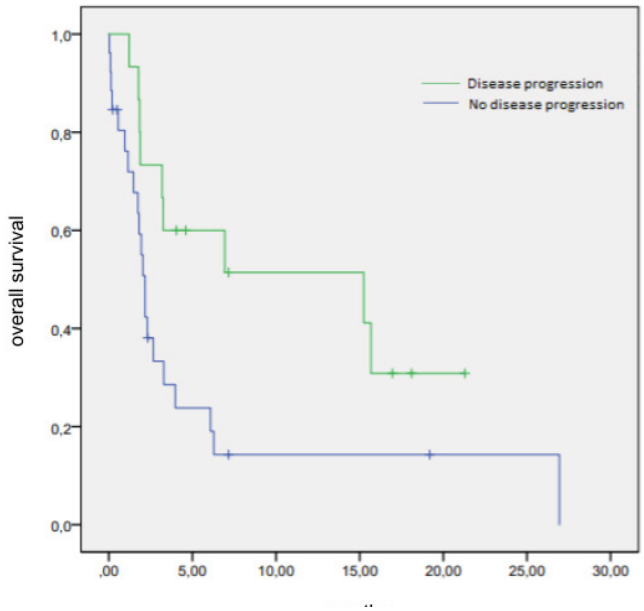

Figure 1: Overall survival according to disease progression at PC's diagnosis.

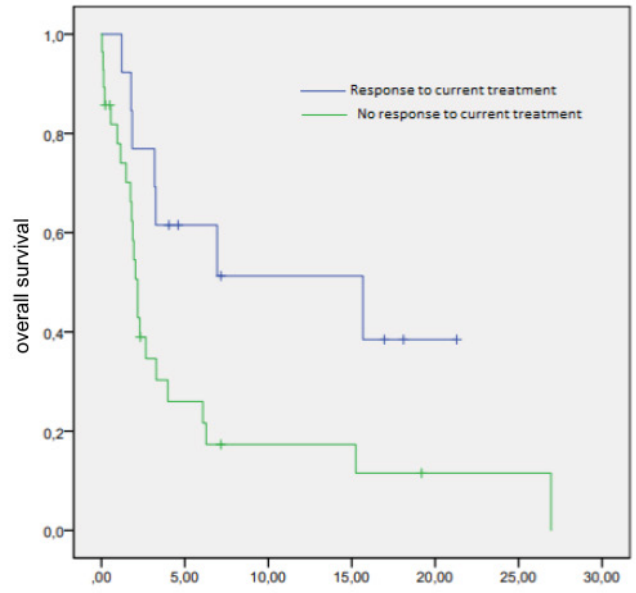

Figure 2: Overall survival according to treatment response at PC's diagnosis.

In terms of laboratory parameters, patients with an AST level ≥ 2 times the upper limit had an OS of 2.2 months, contrasting with 15.2 months for low AST levels (HR 2.9; 95% CI 1.2 - 7.1; p=0.019). A similar significance was noted in AST levels ≥ 5 times the upper limit, with an OS of 0.9 months versus 6.3 months (HR 5.3; 95% CI 2.1 - 13.1; p<0.001). An ALT level ≥ 2 times the upper limit corresponded to an OS of 1.9 months, compared to 3.9 months for low ALT levels (HR 2.4; 95% CI 1.0 - 5.5; p=0.039). No statistical significance was observed for OS when analyzing ALT levels ≥ 5 times. OS for patients with a high bilirubin level (>1.1mg/dL) was significantly lower compared to those with normal values: 1.8 months versus 15.2 months (HR 4.2; 95% CI 1.8 - 9.7; p=0.001). Patients with albumin levels less than 3.5g/dL had a poorer prognosis, with an OS of 1.2 months versus 15.2 months for those with normal values (HR 5.1; 95% CI 1.8 - 14.6; p=0.003).

Regarding the number of endocrine therapy lines before PC diagnosis, patients receiving up to one line had an OS of 6.3 months, compared to 2.2 months for those with two or more endocrine therapies (HR 2.4; 95% CI 1.1 - 5.3; p=0.03). (Figure 3) Previous exposure to ≥ 2 chemotherapy lines before PC diagnosis led to a dismal prognosis compared to fewer lines of chemotherapy (OS 2.2 months versus 26.9 months; HR 3.3; 95% CI 1.4 - 8.2; p=0.008). (Figure 4).

Following the diagnosis of PC, individuals who discontinued their ongoing treatment exhibited an OS of 0.6 months, contrasting with 6.3 months for those who continued treatment (HR 16.1; 95% CI 5.3 - 49.1; p<0.001). While patients maintaining the same treatment experienced a higher OS compared to those who switched treatments (15.7 months versus 3.3 months, respectively), this difference did not reach statistical significance (p=0.12).

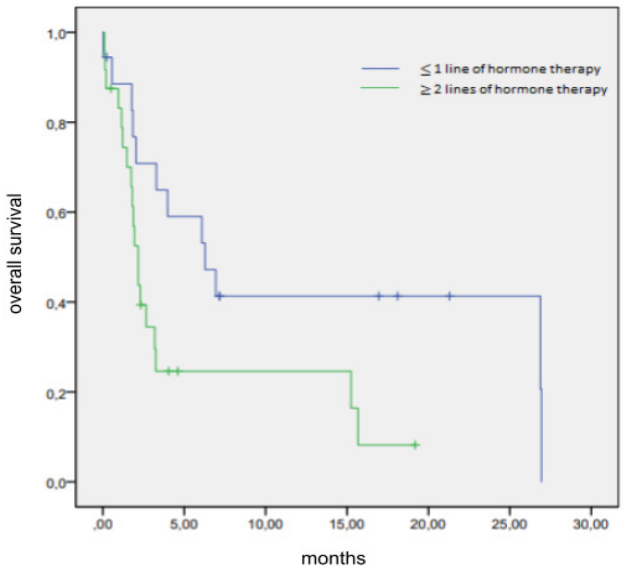

Figure 3: Overall survival according to previous number of lines of hormone therapy.

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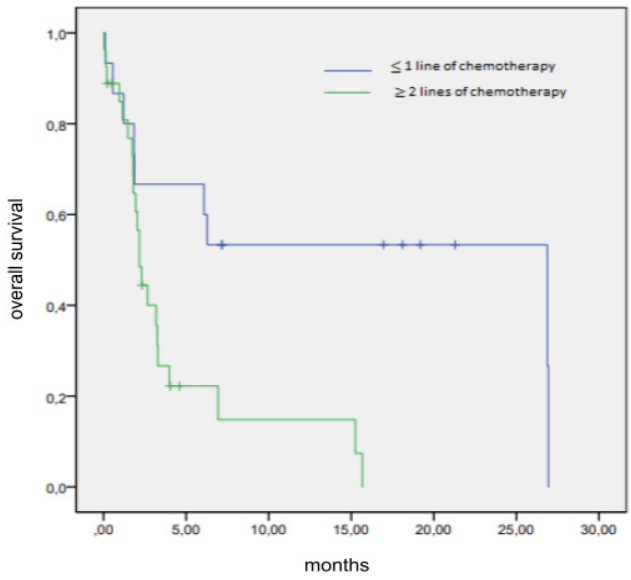

Figure 4: Overall survival according to the previous chemotherapy lines.

Discussion

This study represents the largest reported Latin American series on pseudocirrhosis in breast cancer. Our findings suggest that patients with pseudocirrhosis are typically around 55 years old, and the primary radiological observation is a nodular contour of the liver. These patients often have HR+ metastatic breast cancer and are exposed to more than two lines of chemotherapy, in addition to endocrine therapy. Additionally, pseudocirrhosis can be complicated by portal hypertension and hepatocellular failure at the time of diagnosis. The impact of pseudocirrhosis on patients' ability to tolerate further systemic therapies for breast cancer is significant, leading to poor survival outcomes. However, it is essential to consider that this may be influenced by late diagnosis.

To enhance our understanding of the factors associated with pseudocirrhosis, there is a need to identify higher-risk populations and develop precise assessment tools for targeted treatment approaches. Notably, there are no reported associations between pseudocirrhosis and viral hepatitis or alcohol use [3]. Previous evaluations of pseudocirrhosis have primarily been single-center retrospective studies, emphasizing the need for larger, comprehensive investigations [3,12,14]. Table 3 provides a comparison of demographic, clinical, radiological, pathological, and clinical outcomes across some of the main series on pseudocirrhosis.

Our study aligns with existing literature regarding the demographic characteristics of the population associated with pseudocirrhosis [3,12]. Regarding age and breast cancer subtype, patients are typically around 55 years old and have HR+ metastatic breast cancer in the liver. The correlation between the luminal subtype and pseudocirrhosis remains uncertain. The lower frequency of this complication in HER2-positive or triple-negative tumors may be attributed to their greater aggressiveness, leading to shorter survival and limiting the time for the development of pseudocirrhosis [13]. However, there are variations in radiological descriptions. While the majority of our population (76.7%) presented a nodular contour, this feature was observed in nearly all patients from North American series and only 10% of European series [3,12]. This discrepancy may be attributed to the lack of standardization in radiological evaluations and reports. It is also plausible that undisclosed clinical conditions, such as comorbidities, not accounted for in these studies, could influence some baseline liver conditions.

Despite its fundamental differences from true cirrhosis, pseudocirrhosis can result in shared complications due to structural and functional changes in the liver. In our study, portal hypertension were observed, evidenced by ascites in 50% of cases and varices in 10%, aligning with literature reports of portal hypertension in 11% to 40% of cases [3,12,14]. Approximately half of our patients displayed signs of hepatocellular failure during follow-up, characterized by hyperbilirubinemia (44%) and hypoalbuminemia (60%), consistent with previous series [12]. Hepatocellular failure was associated with poorer OS in North American series [12]. However, factors like hyperbilirubinemia and hypoalbuminemia, along with coagulopathy, could be influenced by cancer-associated cachexia, malnutrition, liver infiltration by metastases, and systemic therapy-induced injury [3,15].

Regarding survival outcomes, the present study indicated lower OS after the diagnosis of PC. However, this could be linked to delayed PC detection, as time to PC diagnosis after breast cancer metastasis was longer in our study compared to North American and European series [3,12]: Despite this, OS from the diagnosis of metastatic disease was similar to the North American series [3].

Pseudocirrhosis prognosis remains dismal, and the optimal approach is unclear, given the uncertain pathogenesis. It may arise from disease progression, treatment response, or systemic treatment toxicity [16-18]. Exposure to two or more lines of chemotherapy or endocrine therapy conferred an increased risk of death, highlighting the association between systemic treatment exposure, pseudocirrhosis, and worse survival in liver metastasis patients.

In this serie of patients, 38.6% developed PC during disease progression, resulting in poorer survival compared to those without progression. PC occurring after treatment response demonstrated better survival, while PC following treatment toxicity showed no significant difference in OS. These findings align with previous series reporting varied treatment outcomes at PC diagnosis. Progressive disease

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was identified in 10.4% and 53.5% of patients, while PR was observed in 52% and 15% in European and North American series, respectively [3,12]. These findings are contentious, considering that capsular retraction can diminish the size of liver lesions without necessarily indicating a treatment response. Additionally, existing literature does not demonstrate a correlation between the number of liver metastases and the occurrence of capsular retraction.

This study had identified that an AST level ≥ 2 and ≥ 5 times the upper limit was associated with worse survival (HR 2.9; 95% CI 1.2 - 7.1; p=0.019 and HR 5.3; 95% CI 2.1 - 13.1; p< 0.001, respectively). Additionally, a high level of bilirubin was negatively correlated with overall survival (HR 4.2; 95% CI 1.8 - 9.7; p=0.001), as were lower levels of albumin (HR 5.1; 95% CI 1.8 - 14.6; p=0.003), indicating the potential utility of these laboratory parameters as prognostic biomarkers.

Determining the most appropriate treatment for patients still fit after PC onset is crucial. Almost 40% of our patients underwent a change in treatment after the occurrence of PC, consistent with prior data [12]. While we observed that treatment interruption was linked to lower survival, it is essential to acknowledge that PC patients often experience substantial performance decline, liver failure, or other complications, limiting the feasibility of continuing cancer treatment and subsequently diminishing survival. Gopalakrishnan et al. noted that 20% of patients transitioned to hospice after PC [12]. In contrast, Engelman et al reported a disease control rate of 50% with new treatment initiated after PC [3]. Therefore, determining prognostic factors becomes essential in effectively selecting patients for further cancer treatment.

Finally, our study has some limitations beyond its retrospective nature. The most notable is the low number

Table 3: Comparison between the largest series in pseudocirrhosis.

N	Simões et al.	Engelman et al. [3]	Gopalakrishnan et al. [12]
	44	48	86
Median age (years)	55.1	50.6	57.5
Subtype			
HR+	84.10%	88.20%	86%
HER2+	11.50%	8.80%	15%
Triple negative	4.80%	2.70%	7%
Previous endocrine therapy	100%	72.90%	85%
Previous chemotherapy lines (median)	2	2	3
Previous breast cancer response			
Complete response	0 (0%)	0 (0%)	2 (2.3%)
Partial response	7 (15.9%)	25 (52.1%)	13 (15.1%)
Stable disease	12 (27.3%)	16 (33.3%)	24 (27.9%)
Progressive disease	17 (38.6%)	5 (10.4%)	46 (56.5%)
Notavailable	8 (18.2%)	2 (4.2%)	1 (1.2%)
Median time from metastatic disease to PC	33.3 months	13.3 months	23.4 months
Liver metastasis	93.20%	97.90%	94.20%
Peritoneal carcinomatosis	20.50%	7.10%	-
Radiologic findings			
Nodular contour	76.70%	10.40%	98%
Capsular retraction	32.60%	-	83%
Irregular contour	11.10%	75%	-
Ascites	50%	58.30%	35%
Varices	10%	22.90%	18.60%
Splenomegaly	-	27.10%	15%
Hyperbilirubinemia	44.40%	64.60%	48%
Hypoalbuminemia	59.30%	75%	-
New treatmentafter PC	43.90%	-	49%
Latter breast cancer response			

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Complete response	-	0 (0%)	-
Partial response	-	16 (33.3%)	-
Stable disease	-	8 (16.7%)	-
Progressive disease	-	11 (22.9%)	-
Not available	-	13 (27.1%)	-
OS after first metastatic lesion	50.4 months	-	50.8 months
OS after PC	3.2 months	8.5 months	10 months

N: number; HR+: hormone-receptor-positive; PC: pseudocirrhosis; OS: overall survival

of histopathological confirmations of pseudocirrhosis (only 3 patients were biopsied), despite all patients presenting characteristic radiological findings and clinical evolution. Another limitation was the failure to formally conduct differential diagnoses of liver cirrhosis, such as autoimmune hepatitis or cirrhosis associated with non-alcoholic fatty liver disease, which is frequent in women using endocrine therapy. Additionally, most imaging tests were not available for standardized assessment by a single radiologist, but all these radiologic findings were reviewed by radiologist. This poses a limitation in our analysis, as the absence of any term in the radiological report does not necessarily mean its actual absence; it may simply not have been highlighted in the report. Despite these limitations, this series stands as one of the largest in terms of case numbers in the literature and provides additional demographic and clinical features of pseudocirrhosis patients.

Conclusion

This study presents one of the largest case series documenting pseudocirrhosis in individuals with metastatic breast cancer within the existing literature. The majority of cases were characterized by invasive ductal carcinoma and the luminal molecular subtype. Ascites emerged as the most prevalent clinical manifestation. Abnormal laboratory findings, including hyperbilirubinemia, elevated transaminases, and hypoalbuminemia, were correlated with a poorer prognosis, and may potentially be used as biomarkers of prognosis. A significant proportion of patients received PC diagnosis during disease progression, and exposure to two or more lines of systemic therapy was linked to a diminished survival rate. Patients not able to undergoing subsequent cancer treatment after PC diagnosis had a more unfavorable disease outcome. Probably, early detection of PC is imperative for the effective management of this complication, and further studies are warranted to corroborate these observations.

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