Diagn Interv Radiol 2023; DOI: 10.4274/dir.2023.232299

ABDOMINAL IMAGING

ORIGINAL ARTICLE

Chemotherapy-associated liver morphological changes in hepatic metastases (CALMCHeM)

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PURPOSE

To review imaging findings in chemotherapy-associated liver morphological changes in hepatic metastases (CALMCHeM) on computed tomography (CT)/magnetic resonance imaging (MRI) and its association with tumor burden.

METHODS

We performed a retrospective chart review to identify patients with hepatic metastases who received chemotherapy and subsequent follow-up imaging where CT or MRI showed morphological changes in the liver. The morphological changes searched for were nodularity, capsular retraction, hypodense fibrotic bands, lobulated outline, atrophy or hypertrophy of segments or lobes, widened fissures, and one or more features of portal hypertension (splenomegaly/venous collaterals/ascites). The inclusion criteria were as follows: a) no known chronic liver disease; b) availability of CT or MRI images before chemotherapy that showed no morphological signs of chronic liver disease; c) at least one follow-up CT or MRI image demonstrating CALMCHeM after chemotherapy. Two radiologists in consensus graded the initial hepatic metastases tumor burden according to number (≤10 and >10), lobe distribution (single or both lobes), and liver parenchyma volume affected (<50%, or ≥50%). Imaging features after treatment were graded according to a pre-defined qualitative assessment scale of "normal," "mild," "moderate," or "severe." Descriptive statistics were performed with binary groups based on the number, lobar distribution, type, and volume of the liver affected. Chi-square and t-tests were used for comparative statistics. The Cox proportional hazard model was used to determine the association between severe CALMCHeM changes and age, sex, tumor burden, and primary carcinoma type.

RESULTS

A total of 219 patients met the inclusion criteria. The most common primaries were from breast (58.4%), colorectal (14.2%), and neuroendocrine (11.0%) carcinomas. Hepatic metastases were discrete in 54.8% of cases, confluent in 38.8%, and diffuse in 6.4%. The number of metastases was >10 in 64.4% of patients. The volume of liver involved was <50% in 79.8% and ≥50% in 20.2% of cases. The severity of CALMCHeM at the first imaging follow-up was associated with a larger number of metastases ($P = 0.002$) and volume of the liver affected ($P = 0.015$). The severity of CALMCHeM had progressed to moderate to severe changes in 85.9% of patients, and 72.5% of patients had one or more features of portal hypertension at the last follow-up. The most common features at the final follow-up were nodularity (95.0%), capsular retraction (93.4%), atrophy (66.2%), and ascites (65.7%). The Cox proportional hazard model showed metastases affected ≥50% of the liver ($P = 0.033$), and the female gender ($P = 0.004$) was independently associated with severe CALMCHeM.

CONCLUSION

CALMCHeM can be observed with a wide variety of malignancies, is progressive in severity, and the severity correlates with the initial metastatic liver disease burden.

KEYWORDS

Liver metastases, pseudocirrhosis, liver tumor burden

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Received 09 May 2023; revision requested 16 May 2023; accepted 30 May 2023.

Epub: 13.06.2023

Publication date: 21.07.2023

DOI: 10.4274/dir.2023.232299

You may cite this article as: Pope MC, Olson MC, Flicek KT, et al. Chemotherapy-associated liver morphological changes in hepatic metastases (CALMCHeM). *Diagn Interv Radiol.* 2023;29(4):571-578.

In recent decades, the number of chemotherapeutic and biological agents employed to treat hepatic metastatic disease has increased exponentially and has resulted in prolonged survival, particularly in metastatic breast cancers.[1] Many of these cytotoxic medications are metabolized in the liver, and systemic chemotherapy-induced hepatotoxicity is a well-recognized complication of treatment, with a spectrum ranging from an asymptomatic elevation of liver enzymes to acute hepatitis.[2,3] The pathological modes of systemic chemotherapy-associated liver injury can be steatosis, chemotherapy-associated steatohepatitis (CASH), and sinusoidal obstruction syndrome (SOS), and these specific changes are related to metabolic byproducts of the agents used.[4]

A specific form of hepatic injury occurs only in the presence of hepatic metastatic disease and in association with systemic chemotherapy.[5-9] This injury possibly results from a desmoplastic reaction surrounding the chemotherapy-treated tumors, repeated tumor shrinkage and enlargement, and reactive nodular parenchymal regeneration following treatment.[10] When progressive, it leads to a scarred and contracted liver that simulates cirrhosis and may be complicated by portal hypertension and ascites.[6] This unique condition was first described as hepatic lobatum carcinomatosum in 1987 by Honma[11] in a case of scirrhous breast carcinoma. Subsequently, this entity was described in several case reports and case series as pseudocirrhosis,[5,7,9,12,13] and the term was applied to describe a constellation of liver findings: fine, diffuse nodularity of the liver surface, multifocal retraction of the hepatic capsule, and caudate lobe enlargement. However, in histopathological specimens, there was a characteristic absence of regenerating nodules and bridging fibrosis, which is typically found in cirrhosis from chronic liver disease.[5,7,9,12,13]

For lack of a better term, non-specific "pseudocirrhosis" continues to be used to describe not only this unique injury but also many other pathologic processes that occur in the liver, such as untreated diffuse hepatic metastases, granulomatous diseases like sarcoidosis and tertiary syphilis, chronic Budd–Chiari syndrome, chronic portal vein thrombosis, schistosomiasis, non-cirrhotic portal hypertension, and nodular regenerative hyperplasia.[13-15] Emerging evidence suggests that pseudocirrhosis may be a misnomer, as many of these patients develop sequelae of portal hypertension, including splenomegaly, formation of portosystemic collaterals, and ascites.

While the imaging and clinical picture may be similar to cirrhosis, the pathologic changes that only occur in post-chemotherapy hepatic metastatic disease could be more properly termed chemotherapy-associated liver parenchymal changes in hepatic metastases (CALMCHeM). CALMCHeM characteristically has normal liver parenchyma between fibrotic bands and no known association with chronic liver disease etiologies. Normal liver function is maintained until late or severe changes occur.

CALMCHeM has mostly been described in breast carcinoma metastatic disease, with few case reports on other primaries.[16-19] Previous studies have described the incidence, prevalence, risk factors, and natural history progression of CALMCHeM and mostly focused on breast carcinoma.[7,9,20] The purpose of our study was to characterize the baseline tumor burden and imaging appearances of CALMCHeM among a broader spectrum of malignancies and evaluate its temporal progression of severity.

Main points

- Chemotherapy-associated liver morphological changes in hepatic metastases (CALMCHeM) can be observed in a wide variety of malignancies.
- CALMCHeM occurs only in the presence of hepatic metastases and following systemic chemotherapy.
- CALMCHeM severity correlates with the metastatic liver disease burden.
- Metastatic liver disease burden is associated with the development of portal hypertension.
- CALMCHeM severity progresses over time and requires follow-up for detection of the development of complications.

Methods

Study cohort

In this Health Insurance Portability and Accountability-compliant, single-institute, multisite retrospective study, we conducted a systematic search of electronic medical records to identify patients with potential imaging features of CALMCHeM. The Institution of Mayo Clinic's Review Board approved the retrospective study (reference: IRB 12-009433) with the waiver of informed consent for its retrospective nature. A proprietary search engine was used to analyze radiology reports from 1995 to 2020. The search matrix included various combinations of the terms "pseudocirrhosis," "metastases," "liver/hepatic," "cirrhosis," "fibrosis," and "nodular contour/nodularity." The more general descriptors in the search were included due to the relatively inconsistent use of "pseudocirrhosis" in clinical notes to describe features of CALMCHeM.

The inclusion criteria were as follows: a) no known chronic liver disease; b) the presence of hepatic metastases on imaging; c) the availability of a contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) image before chemotherapy that showed no morphological signs of chronic liver disease; d) at least one follow-up CT or MRI image demonstrating CALMCHeM after chemotherapy.

The exclusion criteria included adjunctive chemotherapy associated with surgical resection and/or ablation therapy, percutaneous ablation therapy, chemoembolization, and directed radiation therapy due to the potential for confounding morphologic changes that could occur following these treatments. Patients with known chronic liver disease were excluded, as fibrotic or cirrhotic changes can coexist.

Data collection and analysis

Before the radiologists responsible for analyzing the images began data collection, they participated in an online training session to familiarize themselves with the definitions and grading systems used in the study. Following the training session, imaging studies (CT and/or MRI) were reviewed by two radiologists in consensus at all three sites. The burden of hepatic metastases in each case was quantified according to a predetermined grading system (Table 1) that included the number of metastatic lesions (1–5, 6–10, >10), and the estimated volume of the liver affected (0%–25%, >25%–50%, and ≥50%). The qualitative parameters, such as the distribution of lesions [single lobe (right or left) and both lobes] and lesion morphological characteristics (discrete, diffuse, or confluent) were also recorded (Table 1). Follow-up CT and MRI scans performed after treatment initiations were then evaluated sequentially.

Imaging features were graded according to a qualitative assessment scale including "minimal," "mild," "moderate," or "severe" CALMCHeM changes (Table 2), relative to the baseline study (Figure 1). Assessed features included capsular retraction, nodularity, lobulations parenchymal atrophy or hyper-

trophy, widened fissures, splenomegaly, portosystemic collaterals, and ascites. Patients were considered to manifest mild, moderate, or severe changes when one or more features listed in Table 2 were present. Capsular retraction was defined as the focal indentation of the hepatic capsule below the adjacent normal contour of the liver. All follow-up CT/MRI studies were evaluated. The time interval between studies that demonstrated new changes and resulted in the upgrading of the severity score was recorded for a maximum of four follow-up examinations. Therefore, the time intervals for CALMCHeM changes from minimal to mild, mild to moderate, and moderate to severe were recorded. Patient demographics, primary malignancy type, chemotherapeutic agents, and the time interval between changes in CALMCHeM severity were recorded for each case.

Statistical analysis

Descriptive statistics were performed to characterize patient demographics, primary cancer types, and general CALMCHeM feature frequencies. The baseline metastases characteristics into binary groups for each of the following characteristics: number (≤10 and >10), lobar distribution (single or both lobes), type (discrete vs. diffuse or confluent), and volume of the liver affected (<50% vs. ≥50%). Chi-square and t-tests were used for comparative statistics of imaging features at various time points. After the initial analysis of all tumor types, only the four most common primaries were considered for regression analysis, as there were few representative cases in other primaries. Similarly, chemotherapeutic agents were not included in the regression analysis, as different agents and different combinations were used for patients in the study group. The Cox proportional hazard model was used to determine the association between severe CALMCHeM changes and age, sex, tumor burden, and primary carcinoma type. Schoenfeld residuals tests found no violation of the proportional hazard assumption for the Cox model. All statistical analyses were performed using Stata/SE version 16.1 (StataCorp LLC, College Station, TX).

Table 1. Hepatic metastases characteristics at baseline CT or MRI

Characteristic	Classification
Number of metastases	1–5 6–10 >10
Lobar distribution	Right lobe Left lobe Both lobes
Liver volume affected	0%–25% >25%–50% ≥50%
Morphology	• Discrete-with intervening normal liver parenchyma • Confluent-multiple coalescing or fusing without intervening liver parenchyma between the metastasis nodules at one or more locations • Diffuse-multiple tiny nodules with barely visible intervening liver parenchyma

CT, computed tomography; MRI, magnetic resonance imaging.

Table 2. Severity grading of CALMCHeM

Grade	Description
Minimal	Perfusion changes around the metastases
Mild	Mild retraction of capsule Hypodense bands around or replacing metastases No volume loss
Moderate	Retraction of capsule Hypodense bands Nodularity of surface Lobulated liver Mild volume loss (atrophy) compared to prior or baseline study
Severe	Nodularity and lobulated outline of the liver Loss of liver volume Atrophy of segments or lobes Compensatory hypertrophy Widened fissures

CALMCHeM, chemotherapy-associated liver morphological changes in hepatic metastases.

Results

Study cohort

The search results yielded 1,288 patients who met the initial eligibility requirements. The final number of unique patients meeting the inclusion criteria was 219. There were 62 (28.3%) males and 157 (71.7%) females in the cohort, with a mean ± standard deviation (SD) age of 61.4 ± 11.4 years. The most common primary malignancy included breast carcinoma (58.4%), colorectal carcinoma (14.2%), neuroendocrine carcinoma (11.0%), pancreatic adenocarcinoma (3.7%), and cholangiocarcinoma (3.2%). The complete list of primary malignancies is shown in Table 3. The chemotherapeutic agents are summarized in Supplementary Table 1. The mean ± SD duration of follow-up was 695 ± 608.5 days. The most common baseline imaging modality was CT in 213/219 (95.9%) cases, with only six patients having MRI as the baseline imaging modality. CT was also the most common follow-up imaging modality, with only one patient having MRI for three follow-up studies and four patients having only one MRI study during their follow-up.

Baseline imaging findings prior to chemotherapy initiation

Hepatic metastases were discrete in 120/219 cases (54.8%), confluent in 85/219 cases (38.8%), and diffuse in 14/219 cases (6.4%). The metastases were present in both liver lobes in 179/219 cases (81.7%), the right hepatic lobe only in 26/219 cases (11.9%), and in the left hepatic lobe only in 14/219 cases (6.4%). The number of hepatic metastases was >10 in 141/219 cases (64.4%), 6–10 in 23/219 cases (10.5%), and 1–5 in 55/219 cases (25.1%). The volume of the liver affected by metastases was <25% in 115/219 cases (52.5%), >25% to 50% in 59/219 cases (26.9%), and ≥50% in 45/219 cases (20.5%).

CALMCHeM findings

At the first CT or MRI follow-ups where all cases showed CALMCHeM, minimal changes were seen in 16%, mild changes in 58%, moderate changes in 19.2%, and severe changes in only 6.8%. However, at the final follow-up, severe changes were seen in 54.8% of patients, moderate changes in 31.1%, mild changes in 11.9%, and minimal changes in only 2.3%. CALMCHeM at final follow-up included a nodular surface contour in 209/219 (95.4%), focal capsular retraction in 206/219 (94.1%), parenchymal atrophy for 146/219 (66.7%), ascites in 144/219 (65.8%),

widened fissures for 98/219 (44.7%), portosystemic collaterals in 91/219 (41.6%), caudate lobe hypertrophy for 81/219 (37%), and splenomegaly in 56/219 (25.6%). Severe CALMCHeM significantly correlated with collaterals ($P = 0.001$), splenomegaly ($P = 0.014$), and ascites ($P = 0.001$).

Temporal progression in CALMCHeM

There was a progression in the severity of CALMCHeM over time, and this correlated with baseline metastatic disease burden (Figure 2). At the first follow-up, only 6.8% had severe CALMCHeM, which increased to 54.8% at the final follow-up. Among the patients who developed severe CALMCHeM, those with ≥50% liver volume metastatic disease did so earlier than those with <50% volume of the liver affected (370 days vs. 592 days, $P = 0.012$). Similarly, those with confluent or diffuse metastases reached severe CALMCHeM changes significantly earlier than those with discrete metastases (403 days vs. 713 days, $P = 0.013$). Although patients with >10 metastases (430 days vs. 676 days, $P = 0.322$) and bilobar distribution (460 days vs. 584 days, $P = 0.847$) showed a trend to early severe changes, the differences were not statistically significant.

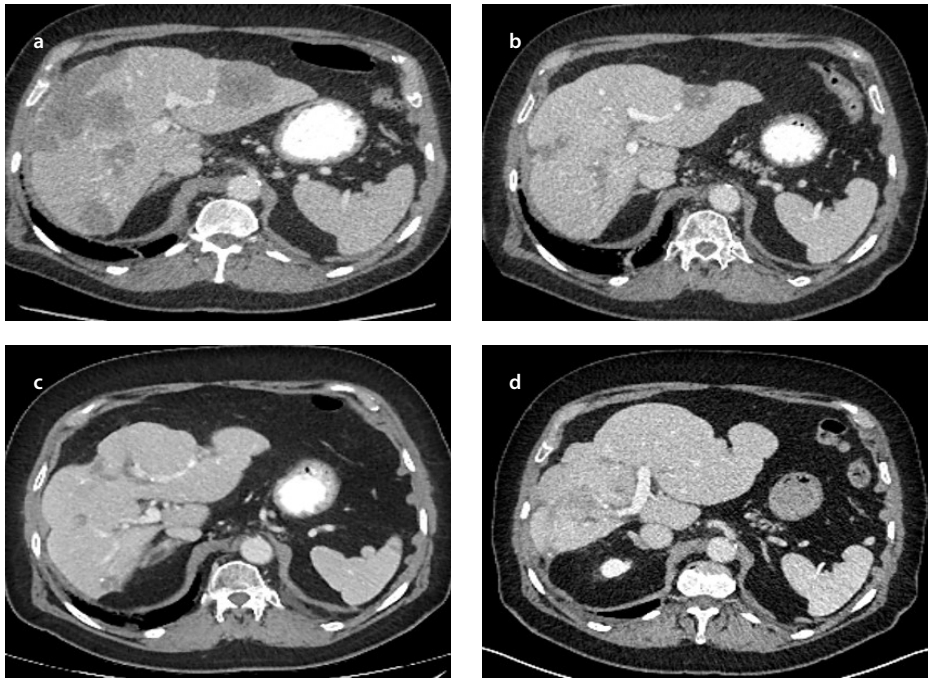

Figure 1. Temporal progression of CALMCHeM in a 72-year-old male with rectal carcinoma and multiple liver metastases. Contrast-enhanced CT images **(a)** before chemotherapy, **(b)** at 3 months, **(c)** at 8 months, and **(d)** at 10 months following systemic chemotherapy (including FOLFOX and bevacizumab). The hepatic metastases were >10 in number, involved both liver lobes, and affected ≥50% of the liver parenchyma. The CALMCHeM changes are mild at 3 months, with retraction of the capsule and some nodularity that progresses to moderate changes at 8 months with a lobulated outline and some atrophy of the right lobe. At 10 months, the changes are severe with significant atrophy of the right lobe and compensatory hypertrophy of the left lobe. CALMCHeM, chemotherapy-associated liver morphological changes in hepatic metastases; CT, computed tomography; FOLFOX, folinic acid, fluorouracil, and oxaliplatin.

Table 3. Primary malignancies in the study group (n = 219)

Primary malignancy	Number	%
Breast carcinoma	128	58.4
Colorectal carcinoma	31	14.2
Neuroendocrine	24	11.0
Pancreatic adenocarcinoma	8	3.7
Cholangiocarcinoma	7	3.2
Gastroesophageal carcinoma	4	1.8
Prostate carcinoma	4	1.8
Lung carcinoma	3	1.4
Leiomyosarcoma	2	1.0
Melanoma	2	1.0
Renal cell carcinoma	2	1.0
Urothelial carcinoma	1	0.5
Thyroid carcinoma	1	0.5
Unknown adenocarcinoma	1	0.5
Parotid carcinoma	1	0.5

Association of tumor burden at baseline with CALMCHeM severity

The proportion of severe changes at the final follow-up was significantly associated with >10 metastases ($P = 0.009$), bilobar distribution ($P = 0.001$), and ≥50% volume of the liver affected ($P = 0.001$). There was no significant association with the morphologic type of metastases. We further evaluated the associations with the four largest metastatic disease types in the study group. This group comprised four main primary carcinomas (breast, colorectal, neuroendocrine, and pancreatic) and a total of 183 cases. Severe changes at the final follow-up were significantly associated with bilobar distribution ($P = 0.006$) and the volume of the liver affected ($P = 0.011$), but not significantly associated with the number or morphologic types of metastases (Table 4, Figure 3). Cox regression analysis was performed in this group and showed that the proportion of cases with severe changes at the final follow-up was significantly associated with the female sex (hazard ratio: 0.46, $P = 0.004$) and volume of the liver affected prior to chemotherapy (hazard ratio: 1.88, $P = 0.033$) (Table 5).

Association of baseline findings with specific CALMCHeM features

Patients with a higher tumor volume at initial presentation had a significantly higher proportion of developed collaterals and splenomegaly. Patients with a ≥50% liver tumor volume, compared to patients with a <50% liver tumor volume, developed more collaterals (64% vs. 37%, $P = 0.001$) and splenomegaly (41% vs. 21%, $P = 0.007$), but there was no difference in ascites (68% vs. 65%, $P = 0.619$). Similarly, patients with >10 metastases, when compared to those with <10 metastases, developed more collaterals (48% vs. 31%, $P = 0.017$) and splenomegaly (30% vs. 16%, $P = 0.017$) but not ascites (66.2% vs. 65%, $P = 0.815$). Patients with bilobar metastases, compared to unilobar metastases,

developed more collaterals (45% vs. 28%, $P = 0.040$) and splenomegaly (28% vs. 13%, $P = 0.042$) but not ascites (67% vs. 63%, $P = 0.632$). Comparing patients with discrete metastases and those with confluent or diffuse metastases, there were no differences in the development of collaterals (40% vs. 44%, $P = 0.5$), splenomegaly (29% vs. 22%, $P = 0.196$), or ascites (64% vs. 68%, $P = 0.586$).

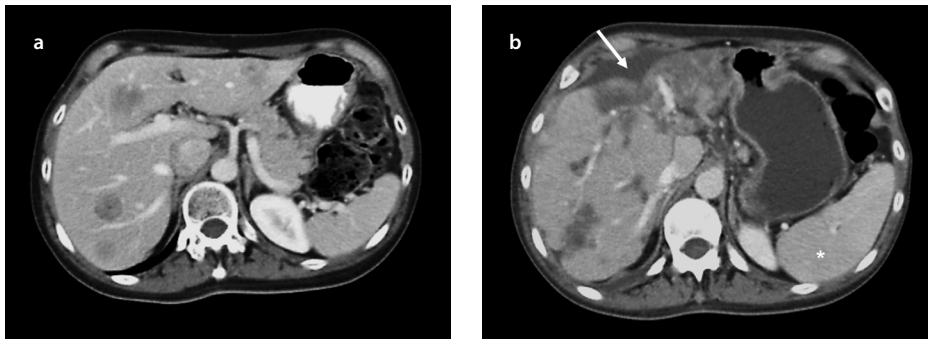

Figure 2. Severe CALMCHeM with portal hypertension. Metastatic infiltrative breast carcinoma in a 52-year-old female with multiple liver metastases. Contrast-enhanced CT images **(a)** before chemotherapy and **(b)** at 23 months following multiple chemotherapy sessions. Severe CALMCHeM changes at 23 months with the development of ascites (white arrow) and splenomegaly (*), consistent with portal hypertension due to CALMCHeM. CALMCHeM, chemotherapy-associated liver morphological changes in hepatic metastases; CT, computed tomography.

Further analyses of the four main cancer types showed similar results. The volume of the liver affected was significantly associated with collaterals ($P = 0.001$) and splenomegaly ($P = 0.032$) but not ascites ($P = 0.652$). Bilobar distribution also showed an association with collaterals ($P = 0.037$) but not splenomegaly ($P = 0.078$) or ascites ($P = 0.294$).

Chemotherapeutic agents and CALMCHeM at the final follow-up

Among the several chemotherapeutic agents used, only the following were significantly associated with severe changes at final follow-up: bevacizumab ($P = 0.038$), cyclophosphamide ($P = 0.022$), docetaxel ($P = 0.019$), doxorubicin ($P = 0.002$), gemcitabine ($P = 0.007$), paclitaxel ($P = 0.027$), and zoledronic acid ($P = 0.046$). When analyzed by the four most common primary malignancy types as a group, significant associations with severe changes were observed

Table 4. Patient characteristics, baseline tumor burden features, and CALMCHeM features at final follow-up in all patients and the four most common primaries

Primary tumor	All (n = 219)	Breast (n = 128)	Colorectal (n = 31)	NET (n = 24)	PDAC (n = 8)
Mean age ± SD (years)	61.4 ± 11.4	61.5 ± 11.8	60.2 ± 11.7	63.3 ± 9.8	63.1 ± 9.4
Male:female	62:157	0:128	21:10	19:5	3:5
Number of metastases					
<10	78 (35.6%)	46 (36%)	8 (25.8%)	3 (12.5%)	4 (50%)
>10	141 (64.4%)	82 (64%)	23 (74.2%)	21 (87.5%)	4 (50%)
Lobar distribution					
Single lobe	179 (81.7%)	25 (19.5%)	2 (6.5%)	0 (0%)	3 (37.5%)
Both lobes	40 (18.3%)	103 (80.5%)	29 (93.5%)	24 (100%)	5 (62.5%)
Volume of the liver affected					
<50%	174 (79.5%)	105 (82%)	20 (64.5%)	18 (75%)	7 (87.5%)
≥50%	45 (20.5%)	23 (18%)	11 (35.5%)	6 (25%)	1 (12.5%)
Type of metastases					
Discrete	120 (54.8%)	74 (57.8%)	14 (45.2%)	13 (54.2%)	6 (75%)
Diffuse/confluent	99 (45.2%)	54 (42.2%)	17 (54.8%)	11 (45.8%)	2 (25%)
Median time to first CALMCHeM (days)	537	155	187	223	214
Median time to severe CALMCHeM (days)	673	493	869	439	430
Capsular retraction	205 (93.6%)	122 (95.3%)	29 (93.5%)	22 (91.7%)	8 (100%)
Surface nodularity/lobulations	208 (95%)	125 (97.7%)	26 (83.9%)	24 (100%)	8 (100%)
Atrophy	145 (66.2%)	91 (71.1%)	15 (48.4%)	20 (83.3%)	7 (87.5%)
Widened fissures	98 (44.75)	66 (51.6%)	10 (32.3%)	12 (50%)	5 (62.5%)
Compensatory hypertrophy	80 (36.5%)	50 (39.1%)	10 (32.3%)	10 (41.7%)	3 (37.5%)
Splenomegaly	55 (25.1%)	28 (21.9%)	13 (41.9%)	4 (16.7%)	1 (12.5%)
Portosystemic collaterals	92 (42%)	50 (39.1%)	13 (41.9%)	11 (45.8%)	5 (62.5%)
Ascites	144 (65.8%)	85 (66.4%)	23 (74.2%)	10 (41.7%)	5 (62.5%)
PHTN	159 (72.6%)	92 (71.8)	26 (83.9%)	13 (54.2%)	6 (75%)
CALMCHeM grade at final follow-up					
Minimal	5 (2.3%)	1 (0.8%)	1 (3.2%)	0 (0%)	0 (0%)
Mild	26 (11.9%)	11 (8.6%)	6 (19.4%)	2 (8.3%)	1 (12.5%)
Moderate	68 (31.1%)	39 (30.5%)	12 (38.7%)	6 (25%)	2 (25%)
Severe	120 (54.8%)	76 (59.4%)	12 (38.7%)	16 (66.7%)	5 (62.5%)

CALMCHeM, chemotherapy-associated liver morphological changes in hepatic metastases; NET, neuroendocrine tumor; PDAC, pancreatic ductal adenocarcinoma; PHTN, portal hypertension, SD, Standard deviation.

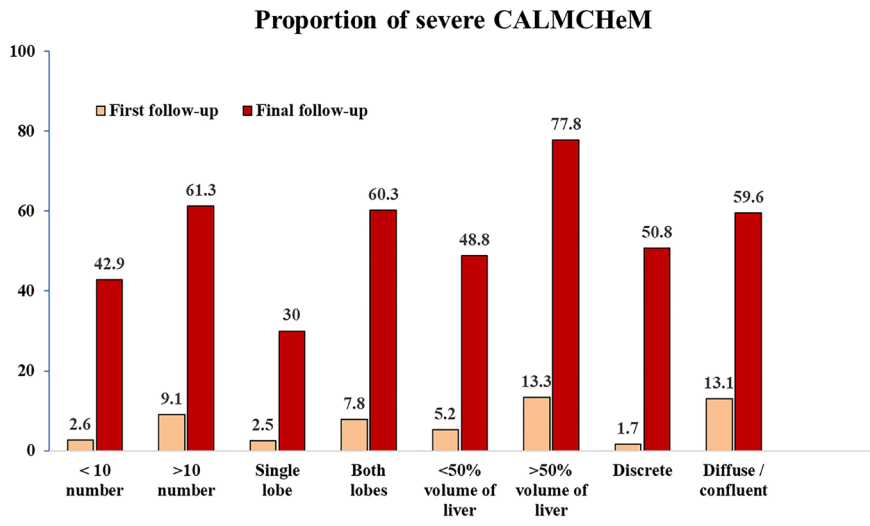

Figure 3. Bar graph showing the proportion of severe CALMCHeM at first and final follow-up imaging vs. the number of metastases, lobe involvement, the volume of the liver affected, and the type of metastases. CALMCHeM, chemotherapy-associated liver morphological changes in hepatic metastases.

Table 5. The hazard ratio for severe CALMCHeM changes in 183 patients (four largest groups of primaries: breast, colorectal, neuroendocrine, and pancreatic)

Characteristic	Hazard ratio	95% CI	*P* value
Female sex	0.46	0.28–0.78	0.004
The volume of the liver affected	1.88	1.05–3.01	0.03

CALMCHeM, chemotherapy-associated liver morphological changes in hepatic metastases; CI, confidence interval

with docetaxel (P = 0.022), doxorubicin (P = 0.001), gemcitabine (P = 0.002), paclitaxel (P = 0.014), and zoledronic acid (P = 0.031). Chemotherapeutic agents were not included in the regression analysis, as different agents and combinations were used in different patients.

Discussion

In this study, we showed that CALMCHeM occurred in metastatic liver disease from a variety of primary malignancies and that the severity of CALMCHeM correlated with tumor burden, primarily the volume of the liver affected. We also showed that these changes were progressive, and the progression to severe changes was also related to the tumor burden. Regression analysis showed a significant association between the female sex and a higher initial volume of hepatic disease with disease severity.

Breast carcinoma was the most common tumor associated with severe CALMCHeM. Several of the previous case reports and case series reported breast carcinoma as the most common cause of CALMCHeM.[5,7,9,21] Possible reasons for CALMCHeM reports with breast carcinoma include the longer survival of the patients with breast carcinoma metastases and the fact that, usually, hormone receptor-positive breast cancer patients are on systemic therapy for longer periods, which may allow for the CALMCHeM to manifest during follow up.[22,23] However, our study confirmed that these changes could also occur in hepatic metastatic disease from other primaries, and we postulate that, in the future, it may be seen more commonly in other metastatic diseases, given the advances in the chemotherapy regimens and, accordingly, the prolonged survival of patients.

Our study analysis shows that tumor burden is the most important factor for predicting the severity of CALMCHeM. A larger tumor burden was observed in cases comprising >10 metastases, bilobar distribution, and a larger volume of the liver parenchyma affected by the metastases. We hypothesize that it is possibly due to the large volume of the liver parenchyma affected by the desmoplastic changes around the metastases, resulting in scarring with accompanied vascular changes that overwhelm the regenerative capacity of the liver parenchyma, and subsequently portal hypertension. The influence of other coexistent liver diseases, particularly fatty liver, diabetes, hypertension, and excessive alcohol intake on the development of CALMCHeM, is not well known. In one study on breast carcinoma metastases by Huppert et al.[22], the study population had a very low incidence of fatty liver or other risk factors, and the researchers concluded that the presence of other risk factors may not be a significant driver of CALMCHeM. Other risk factors may modify CALMCHeM manifestation, as patients with reduced hepatic function reserve are less likely to be candidates for hepatotoxic chemotherapeutic agents and multiple chemotherapy drug regimens.

Although a common finding, ascites was not significantly associated with severe CALMCHeM, which may be explained by the fact that lymphatics and the hepatic functional reserve are preserved in most of the patients, even those with severe CALMCHeM. There may be other reasons for ascites, such as chemotherapy and the presence of peritoneal metastases. Ascites in patients with cirrhosis from chronic liver disease is usually a sign of hepatocellular failure and signifies the progression of the disease. However, the literature shows that ascites is a common finding in patients developing CALMCHeM, but preserved liver function until late stages, similar to our experience. Additionally, there is a very low incidence of hepatic encephalopathy in this population.[21] It is also possible that an increased report of ascites is due to the detection of free fluid in these patients on imaging. Interestingly, in a series by Huppert et al.[22] studying breast carcinoma patients, ascites was associated with a worse median overall survival rate from the time of diagnosis of the metastatic disease. More prospective studies are required to validate this finding.

In our study, patients with a tumor burden ≥50% liver volume and those with diffuse or confluent metastases developed severe CALMCHeM significantly earlier than those who had a smaller liver volume affected or had discrete metastases. This may be explained by the involvement of a larger volume of metastases resulting in the exposure of a larger volume of liver parenchyma to chemotherapy-induced changes which, in turn, cause a larger response of nodular regenerative hyperplasia[5] and perilesional fibrosis, resulting in the faster development of severe changes. Similarly, diffuse confluent metastases are likely to be infiltrative and, accordingly, result in more desmoplastic reaction.[8,24]

Portal hypertension is seen in a significant number of patients with CALMCHeM. In our study population, 73% developed portal hypertension, similar to a recent meta-analysis that showed 80% of patients developed

portal hypertension.[21] In this meta-analysis, there was no further analysis regarding tumor burden parameters. However, in our study, we showed that portal hypertension (splenomegaly and venous collaterals) was related to tumor burden.

Furthermore, we found an association between some chemotherapeutic agents such as docetaxel, doxorubicin, and paclitaxel, with severe CALMCHeM. Although the precise reasons are not clear, doxorubicin and paclitaxel are known to be associated with nodular regenerative hyperplasia.[21,25-27] Several patients received multiple drugs, and some of the association may be due to their concomitant use with chemotherapeutic agents that are known to cause nodular regenerative hyperplasia.

This study has limitations. First, we searched for our cases using radiology reports, and cases with mild CALMCHeM may have been missed or underreported and, hence, excluded from the search. However, CALMCHeM is mainly a radiological diagnosis, which is why we used this approach. Pathological proof of metastases and CALMCHeM in the liver was not available in all the patients, and it was not clinically necessary to perform a liver biopsy for confirmation in these patients. Although we have postulated that the changes occurred due to perilesional fibrosis, histological proof was not available in all patients, and it was impractical or clinically indicated that a liver biopsy was necessary for confirmation in these patients. However, existing studies have implicated perilesional fibrosis as a potential cause of these changes.[5,7,9,11,12] The imaging interval for the heterogeneous group of patients varied, as this was a retrospective study with scans completed per clinical indication and as needed. The time interval for the development of severe CALMCHeM may thus have been affected by the scanning intervals. We did not compare our study cohort with those who did not have hepatic metastases; however, Oliai et al. demonstrated CALMCHeM changes do not occur in the absence of hepatic metastases.[9]

It is difficult to determine the outcome of CALMCHeM in our study, as the population was heterogeneous in terms of primary disease, the chemotherapy regimen received, and the presence of metastatic disease elsewhere in the body. Patients with CALMCHeM rarely develop the complication of liver failure, as they usually do not have chronic liver disease, or chemotherapy is not administered if the liver functions are abnormal. We did not evaluate patients with known chronic liver disease, as doing so would confound with the morphological features evaluated. Studies have shown that CALMCHeM changes in patients could result in portal hypertension and its associated complications.[9] Furthermore, studies have also indicated that survival is shorter in patients with CALMCHeM who develop ascites.[21,22] However, this needs to be confirmed in future studies and possibly with a prospective subject population.

Some of the changes may have been caused by CASH and SOS, particularly in patients with long-term follow-ups. We could not confirm the presence of hepatic steatosis or SOS with imaging, as most patients only received a single portal venous phase scan. The presence of these changes alongside CALMCHEM could not be completely excluded, and their contribution to the severe changes could not be separately assessed.

In conclusion, our study highlights that CALMCHeM changes occur in all malignancies, are progressive in many, and are associated with the development of portal hypertension. The temporal progression and severity of CALMCHeM are associated with the initial burden of liver metastatic disease. Early recognition of CALMCHeM by radiologists can help alert clinicians to possible progression, which may be useful information for clinical decision making about systemic chemotherapy. CALMCHeM is possibly a more appropriate term to use in patients with hepatic metastatic disease, as the appearance of pseudocirrhosis can be caused by several other etiologies. Furthermore, many patients with CALMCHeM develop portal hypertension with preserved hepatic function.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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Supplementary Table 1.
Chemotherapeutic agents

Agent used	Number of subjects
Paclitaxel	95
Capecitabine	83
Gemcitabine	58
Fulvestrant	56
5-fluorouracil	55
Oxaliplatin	49
Folinic acid	47
Carboplatin	41
Bevacizumab	40
Cyclophosphamide	37
Doxorubicin	36
Letrozole	33
Palbociclib	33
Irinotecan	32
Docetaxel	31
Exemestane	29
Anastrozole	28
Zoledronic acid	26
Everolimus	23
Trastuzumab	23
Tamoxifen	20
Denosumab	18
Cisplatin	17
Eribulin	15
Vinorelbine	15
Pertuzumab	14
Panitumumab	11
Goserelin	9
Temozolomide	9
Ixabepilone	8
Cetuximab	7
Etoposide	7
Octreotide	6
Sandostatin	6
Abemaciclib	5
Lapatinib	5
Sunitinib	5
TAS	5
Endoxifen	4
Erlotinib	4
Leuprorelin	4
Methotrexate	4
Alisertib	3
Dacarbazine	3
Megestrol acetate	3
Pazopanib	3
Pemetrexed	3
Ramucirumab	3
Regorafenib	3
Ribociclib	3
Atezolizumab	2
Bicalutamide	2
Lanreotide	2
Pembrolizumab	2
Sirolimus	2
Streptozotocin	2
Telotristat	2
Temsirolimus	2
Vincristine	2
Afatinib	1
Albociclib	1
Anthracycline	1
Bortezomib	1
Brostallicin	1
Cabazitaxel	1
Cabozantinib	1
Cixutumumab	1
Durvalumab	1
Enzalutamide	1
Epirubicin	1
Estradiol	1
Evofosfamide	1
Falsodex	1
Fluoxymesterone	1
Ikpilimumab	1
Interleukin-2	1
Ipilimumab	1
Leuprolide	1
Levatinib	1
Mitoxantrone	1
Nivolumab	1
p38 MAP kinase inhibitor	1
Pamidronic acid	1
Phenylalanine mustard	1
Pixantrone	1
Poziotinib	1
Quarfloxin	1
Rovalpituzumab	1
Silmitasertib	1
Tanespimycin	1
Trabectedin	1
Tremelimumab	1
Triapine	1
Vandetanib	1
Varililumab	1
VEGF	1
Venlavaxine	1
Vismodegib	1