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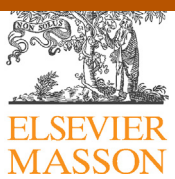

SHORT ORIGINAL ARTICLE / *Gastrointestinal imaging*

# Hepar lobatum carcinomatosum associated with liver metastases from breast cancer: Report of five cases

N. Alberti[a,*], D. Bechade[b], F. Dupuis[c], A. Crombe[d], A. Neuville[c], M. Debled[b], J. Palussiere[a], X. Buy[a], J.-T. Perez[a], M. Desjardin[b], N. Frulio[d], M. Kind[a]

[a] *Department of Radiology, Institut Bergonié, Comprehensive Cancer Center, 229, cours de l'Argonne, 33000 Bordeaux, France*
[b] *Department of Oncology, Institut Bergonié, Comprehensive Cancer Center, 229, cours de l'Argonne, 33000 Bordeaux, France*
[c] *Department of Pathology, Institut Bergonié, Comprehensive Cancer Center, 229, cours de l'Argonne, 33000 Bordeaux, France*
[d] *Department of Radiology, CHU de Bordeaux, Hôpital Saint-André, 1, rue Burguet, 33075 Bordeaux, France*

**KEYWORDS**
Liver;
Liver metastases;
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**Abstract**
*Backgrounds and aims:* Hepar lobatum carcinomatosum (HLC) is an exceptional acquired hepatic distortion which consists in irregularly lobulated hepatic contours seen in patients with known liver metastases, usually from breast carcinoma. We aimed to describe and analyze five similar cases of HLC resulting from metastatic mammary carcinoma in the liver and associated with rapid hepatic failure.
*Methods:* Five cases of HLC were investigated. Medical (including blood liver tests), radiological and histological data (2 cases) were collected and retrospectively analyzed. All patients were followed up for metastatic invasive ductal carcinoma of the breast and had a common pattern of treatment with combination of targeted therapies (bevacizumab, AVASTIN) and chemotherapy (paclitaxel, TAXOL).
*Results:* All the patients showed rapid hepatic failure after a mean of 9 courses of bevacizumab/paclitaxel. In all cases, liver imaging revealed liver capsule retraction and an irregular lobular margin. An apparent tumor regression of all liver metastases was showed in two cases. Biopsies were consistent with sinusoidal obstruction syndrome (SOS) and, surprisingly, no tumoral cells were found.

* Corresponding author.
*E-mail address:* nicoalbertibdx@gmail.com (N. Alberti).

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*Conclusion:* Although rare, such an unusual pattern of liver metastasis may mimick acute cirrhosis and cause rapid hepatic failure in patients, despite possible apparent tumor regression on imaging. The etiology of this pathology is unclear, and may involve multiple pathogenic factors. Direct or indirect vascular injury plays an important role in the development of HLC.


## Abbreviations

| | |
|---|---|
| HLC | Hepar lobatum carcinomatosum |
| CMM | Positron emission tomography—computed tomography |
| SOS | sinusoidal obstruction syndrome |
| NRH | nodular regenerative hyperplasia |

## Introduction

Hepar lobatum carcinomatosum (HLC) is defined as an acquired hepatic distortion consisting of an irregularly lobulated hepatic contour seen in patients with liver metastases, usually from breast carcinoma. Only a very few cases have been described in the literature [1—8]. In this article, we report the largest series of five similar cases of HLC in patients treated for liver metastases from ductal breast carcinoma and associated with rapid hepatic failure. All patients had a common pattern of treatment with combination of targeted therapies (bevacizumab, avastin) and chemotherapy (paclitaxel, taxol).

## Methods

We identified five patients with HLC from April 2013 to May 2014 in the database of our imaging department. Medical (including blood liver tests), radiological and histological data were collected and retrospectively analyzed. This retrospective study had the approval of our Research Ethics Board for chart review and all patients provided written informed consent.

### Computed tomography (CT): all the cases

CT scans were performed with a 16-slice multidetector row helical CT scanner (LightSpeed; GE Medical Systems) with 1.25-mm collimation at 120 kV and 350 mA. Contiguously reconstructed sections were obtained through the abdomen in a single breath-hold with injection of a contrast medium. For contrast-enhanced studies, patients received 100 mL of the contrast material [Iopamiron 370 (Bracco SpA, Milan, Italy) or Ultravist 370 (Bayer Schering Pharma AG, Berlin, Germany)] at a flow rate of 2—3 mL/s.

### Positron emission tomography—computerized tomography (PET—CT): case # 2

After at least 6 h of fasting and capillary glycaemia measurement (less than 2.0 g/L), we injected 5 MBq/kg of $^{18}$F-FDG intravenously. Median uptake delay was 70 min (54—161 min). Whole-body PET/CT images were obtained on a PET scanner Discovery ST (General Electric Medical System, Milwaukee, USA) in 3D mode, without septa. CT transmission scans were acquired previously to the PET scanner for attenuation correction, without oral or intravenous contrast injection, with the constants of 140 kV/80 mAs and slices of 3.75 mm.

### Histological analysis: cases # 4 and 5

On ultrasound, the hepatic parenchyma displays important heterogeneous attenuation, without clearly identified focal mass. We decided to perform percutaneous non-targeted needle biopsies under ultrasonographic guidance using an 18-Gauge needle, according to the recommendations of the American Association for the Study of Liver Diseases. There was no contraindication at the time of the biopsies. Three cores of liver tissue were obtained in each patient. The biopsy specimens were processed and paraffin sections were stained with HES, Masson's trichrome, Perls. An immunochemistry study was performed with anti-Pancytokeratin antibody (AE1/AE3/PCK26 clone, Ventana-760-2135, revealed with ultraView universal DAB detection kit, on Ventana Benchmark Ultra staining system). For the remaining patients, percutaneous biopsies were avoided due to the risk of haemorrhage. Trans-jugular biopsies were also not possible (refusal for patients #1 and #3, lack of cooperation for patient #2).

## Results

### Clinical findings

This study included five female patients with a mean age of 61 years (range 56—69), diagnosed from April 2013 to January 2014. The patients were followed up for metastatic invasive ductal carcinoma of the breast (grade III for cases #1,2 and 4, grade II for cases #3 and 5) with metachronous liver metastases, treated by the combination of targeted therapies (bevacizumab, avastin) and chemotherapy (paclitaxel, taxol).

Patients #1, #2, #3, #4 and #5 were admitted for major asthenia after 6, 10, 9, 10 and 8 courses of bevacizumab/paclitaxel, respectively. Physical examination showed hepatomegaly and signs of hepatocellular failure, including mainly hepatic encephalopathy, stellar angiomas and palmar erythrosis in all patients; jaundice was noticed in patients #1, 2, 4 and 5. In case #1, gastric fibroscopy revealed oesophageal varices (grade I/II).

## Biological results

Last blood tests revealed thrombocytopenia and liver tests showed decreased factor five (42, 58, 30, 50 and 56, respectively) associated with low prothrombin ratio (45, 57, 35, 52 and 48%, respectively), increased serum levels of bilirubin (40, 36, 38, 45 and 38 μmol/L, respectively), glutamyl-transpeptidase, alkaline phosphatase, aspartate and alanine aminotransferases. The mean level of CA 15-3 was 810 U/mL (1673, 1179, 360, 268 and 28 for cases #1, #2, #3, #4, #5, respectively) (normal range < 25 U/mL).

There was no clinical or serological evidence for hepatitis B or C virus infection, autoimmune hepatitis, Wilson's disease, or hemochromatosis; moreover, there was no history of alcohol or drug consumption. Syphilis serum tests, including venereal disease research laboratory test; treponema pallidum hemagglutination assay; and fluorescent treponemal antibody absorption test were also negative.

## Imaging findings

In all cases, CT scans revealed a heterogeneous liver parenchyma, with major capsular retractions that had not been detected on previous scans (performed less than 3 months before radiological diagnosis in all cases) (Figs. 1—3). The retractions were more significant on sites of metastases (case #4, Fig. 3). Imaging revealed an apparent tumor regression of all liver metastases in cases #3 and 4, whereas in cases #1, #2 and #5, lesions were stable. Partial portal vein thrombosis appeared in case #1; suprahepatic veins were patent. While moderate ascites were found in all patients, patent para-umbilical vein was only seen in case #3. No splenomegaly was found. Regional changes included segmental hypertrophy involving the lateral segments (II, III) of the left lobe in all cases, and caudate lobe hypertrophy and central atrophy in cases #1 and 3. Patients #3 and #5 presented a stable disease, whereas patients #1, 2 and 4 suffered from metastatic progression to bone (case #1) and lung sites (cases #2 and #4).

In case #2, PET—CT showed an intense accumulation of $^{18}$F-FDG in sub-capsular regions two months before capsular retractions and regional changes (Fig. 2).

## Pathological results

Percutaneous biopsies were performed in only two patients (cases #4 and #5). Interestingly, no tumor infiltration was revealed by microscopic and immunochemistry study, both in the parenchyma and in the vascular structures. The hepatocyte plates appeared disrupted irregularly widened, reaching an aspect of diffuse nodular regenerative hyperplasia (NRH). These plates were separated by angulous and patchy dilatated sinusoid capillaries; the endothelial cells boarding these sinusoids were focally hyperplasic. Few erythrocytes were spilled between hepatocytes. Centrilobular veins, portal areas and bile ducts were without histological peculiarities, and no fibrosis was observed. All these aspects were consistent with sinusoidal obstruction syndrome (SOS) (Fig. 4).

## Outcome and follow-up

All five patients died of liver failure within 4 weeks of being diagnosed with HLC.

# Discussion

In this paper, we describe the largest series of HLC in patients treated for liver metastases from ductal breast

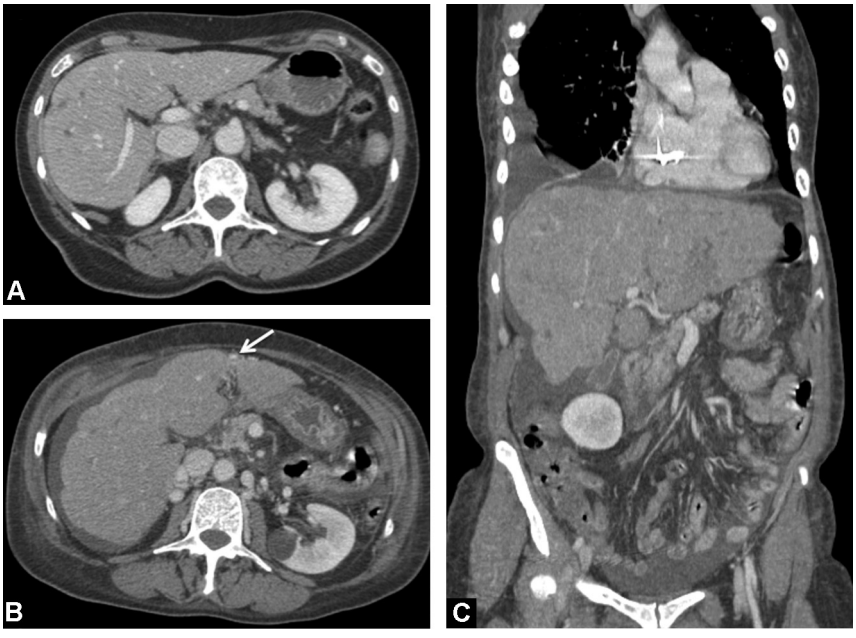


**Figure 1.** Case #3, CT scans. A. A 59-year-old patient with liver metastases (black arrows) secondary to an invasive ductal carcinoma of the breast. B and C. Two months later, CT scan revealed large capsular retraction associated with moderate ascites and patent para-umbilical vein (white arrow). The patient died of hepatic failure 3 weeks later.

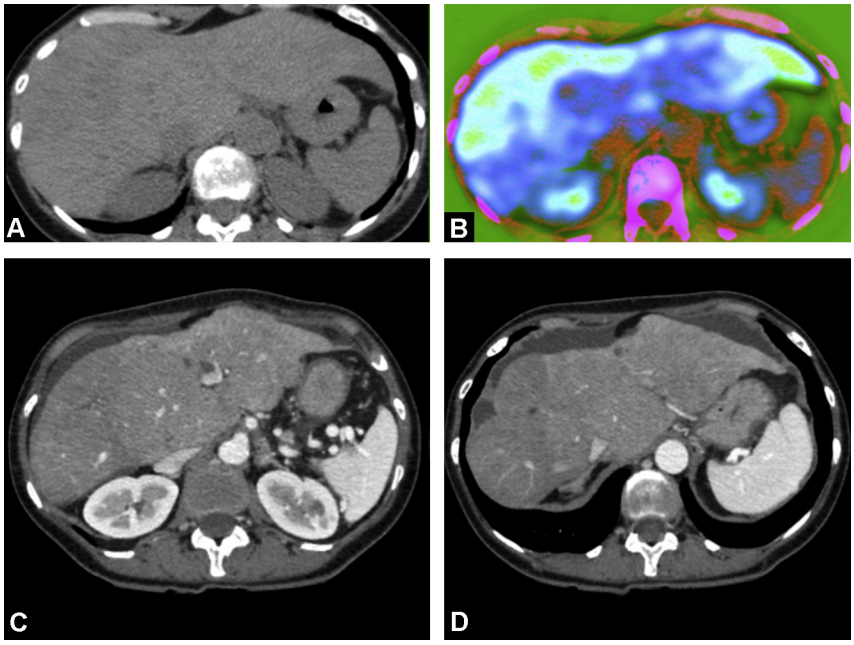


**Figure 2.** Case #1. A. Non-enhanced CT scan of a 56-year-old patient with liver metastases secondary to an invasive ductal carcinoma of the breast. B. PET scan revealed an intense uptake of the sub-scapular areas. C and D. Two months later, CT scan showed large capsular retraction and regional changes, including hypertrophy of caudate lobe (white arrow). Moderate ascites was also observed. The patient died of hepatic failure 4 weeks later.

carcinoma with combination of targeted therapies (bevacizumab, avastin) and chemotherapy (paclitaxel, taxol). All five patients died of acute liver failure within 4 weeks of being diagnosed with HLC.

First described in tertiary syphilitic liver [1], HLC, also known as ''liver pseudocirrhosis'' is often associated with invasive ductal and lobular breast carcinoma [2—5]. Liver metastases from the kidney, stomach, nasopharynx cancers have also been associated to that pathology [6] and, in some rare cases, HLC may reveal the primitive neoplasm [3].

The pathogenesis of HLC is unclear and probably multifactorial. On biopsies, we found similar lesions relative to SOS. Early studies supported the hypothesis that metastatic cell invasion provokes a desmoplastic stromal reaction. In

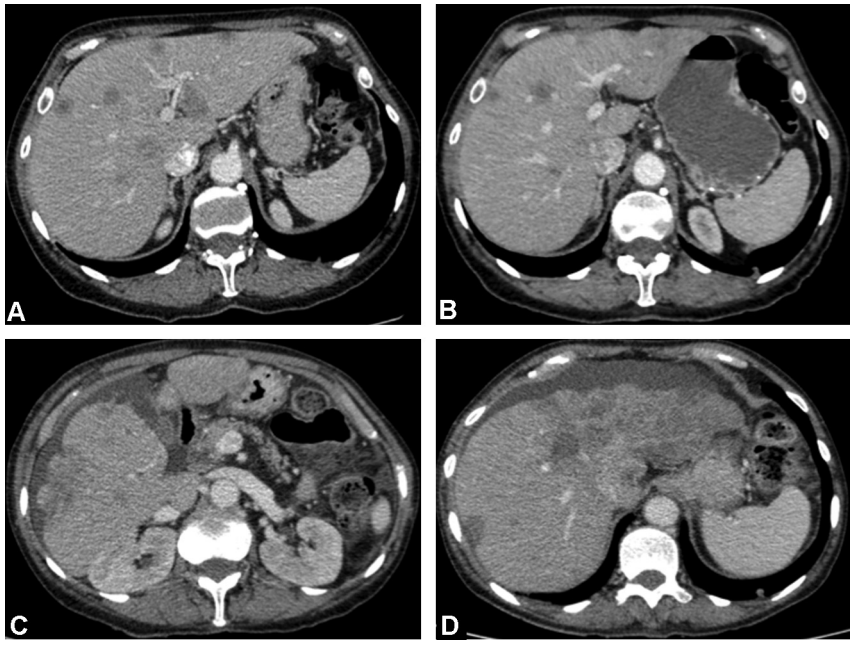


**Figure 3.** Case #5. A. A 69-year-old patient with liver metastases secondary to an invasive ductal carcinoma of the breast. B. Three months later, first retractions occurred, mainly at sites of metastases. An apparent tumor regression of all liver metastases was observed. C. Two months later, these retractions increased significantly. The patient died of hepatic failure 3 weeks later.

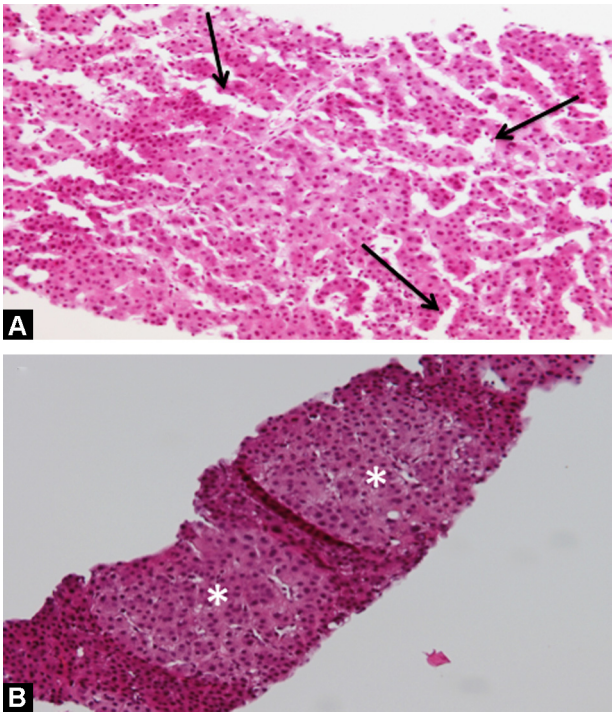


**Figure 4.** Case #5, pathology. Percutaneous biopsies were performed in patient #5. A. Patchy periveinular sinusoidal dilatation (black arrows) and congestion associated with hyperplasic endothelial cells, sometimes unsticked from space of Disse, were observed. Interestingly, nor tumor infiltration or fibrosis were noticed. B. Showed a typical aspect of diffuse NRH (asterisks). All these lesions were consistent with SOS.

several cases, direct invasion and occlusion of intrahepatic vessels, mostly portal and sinusoidal, by tumor cells have been observed [7—10]. However, in our 2 cases, the striking microscopic finding was areas of sinusoidal dilatation which did not show any occlusion by tumor emboli. This vascular injury would be responsible for a heterogeneous liver perfusion with atrophy of the invaded liver segments and compensatory hypertrophy [5,6]. Many chemotherapy drugs, including alkylating agents (cyclophosphamide), anti-metabolites (methotrexate, 5-FU), cytotoxic antibiotics (doxorubicin, epirubicin, mitomycin, mitoxanthrone) and plant alkaloids (vinblastine, paclitaxel, docetaxel) have been associated to SOS [3,8—10]. In our patients, capsular retractions on CT were detected after a mean of eight courses of bevacizumab (avastin)/paclitaxel (taxol). Thus, even though the dose was within the ordinary range used to treat breast cancer, it seems likely that this combination chemotherapy played a role in the development of HLC. A weakness of our study is the lack of percutaneous biopsies, which we avoided due to major hemorrhagic risks associated with hepatic failure in three patients. However, it is likely that such lesions would have been found in the liver of the remaining patients (similar cases: age; type of cancer; clinical, biological and radiological findings).

Liver imaging made the diagnosis in all the cases, showing major liver capsule retraction and an irregular lobular margin with crevices and linear depression. Segmental volume loss and caudate lobe enlargement were observed, as in cirrhosis, in cases #1 and 3. As previously described, retraction occurred mainly at sites of metastases [5]. Signs of portal hypertension are frequently observed in HLC, as in case #3 (patent para-umbilical vein). Interestingly, in case #2, PET—CT showed an intense sub-capsular uptake two months before capsular retractions and regional changes. To our knowledge, this aspect has never been reported in the literature before. MRI may also be useful to support this diagnosis, showing large fibrous bands on delayed-phase defining the pseudo-nodules occurs at initial sites of metastases [5].

Drug-induced liver injury presents with extremely diverse histological patterns, including necro-inflammatory, cholestatic, steatotic and vascular patterns. SOS also referred to as toxic sinusoidal injury, veno-occlusive disease or ''blue liver syndrome'', is a commonly recognized vascular pattern of drug-induced liver injury [7]. For the pathologists, it is characterized by the loss of sinusoidal wall integrity with sinusoidal congestive obstruction, and maybe associated with peri-sinusoidal fibrosis, centrilobular hepatic vein fibrotic obstruction, nodular regenerative hyperplasia (HNR), or peliosis.

In the literature, different therapeutic approaches were adopted to treat HLC, namely, chemotherapy or hormonotherapy; however, the survival of the reported cases never exceeded a few months [11].

## Conclusion

To conclude, we describe five cases of an uncommon liver dysmorphy resulting from liver metastases of breast carcinoma treated with the combination of bevacizumab (avastin) and paclitaxel (taxol). Such an unusual pattern of liver metastasis may mimick cirrhosis and cause rapid hepatic failure in patients, despite apparent tumor regression on imaging. This observation suggests that:

- direct or indirect vascular injury plays an important role in the development of HLC;
- HLC may arise as a particular form of healing and scarring after tumor regression, as previously mentioned [2,3];
- the administration of this particular combination played a role in the development of this affection in our cases [3,4].

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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