

CASE REPORT

Fibrolamellar hepatocellular carcinoma with ovarian metastasis – an unusual presentation

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Abstract

Aim: Fibrolamellar carcinoma (FLC) has been considered a distinct clinical entity vs. hepatocellular carcinoma, with respect to its epidemiology, etiology, and prognosis. **Case presentation:** We describe the unusual case of a 23-year-old female patient with FLC and ovarian (Krukenberg) and peritoneal metastases, clinically mimicking an ovarian carcinoma. Multiple recurrences occurred despite initial R0 resection and chemotherapy, requiring surgical treatment. The patient survived five years and died from generalized disease. **Discussion:** The particularities of our case are discussed by comparison with the other two similar cases and other data from the literature. **Conclusions:** To our knowledge, the ovarian involvement encountered in our case is the third case published in literature, being explained by the superficial location of the liver tumor.

Keywords: fibrolamellar carcinoma, ovarian and peritoneal metastases, surgery.

Introduction

Fibrolamellar carcinoma (FLC) was initially described by Edmondson, in 1956, as a rare pathological variant of hepatocellular carcinoma (HCC) [1]. It represents around 1% of HCC cases [2] and has peculiar histological aspect, which consists of large polygonal eosinophil, well-differentiated malignant hepatocytes, with macronucleoli, included in a fibrous stroma, arranged in thin parallel lamellae [3]. It is usually diagnosed in adolescents and young patients and is not associated with underlying liver disease (e.g., cirrhosis). Therefore, patients present with disease in advanced stages, with large tumors invading adjacent structures. The alpha-fetoprotein (AFP) is not increased. Calcifications and a central scar are revealed on computed tomography (CT) scans. Lymph node metastases are more frequent than in HCC [4]. Extrahepatic spreading may be diagnosed at presentation in one-third of the patients [5]. Prognosis and survival was considered to be better when compared to HCC patients but recent studies [6, 7] indicate that, if HCC patients with cirrhosis are excluded, the outcome is similar.

Half of the patients have lymph node metastases by the time of the initial operation [8] and there are reported cases with peculiar initial presentation due to extrahepatic metastases as pancreatic [9] or pericardial [10]). To date, there are only two cases described in literature of a FLC metastatic to the ovary [11–13].

Herein we present a young patient with ovarian and peritoneal metastases mimicking a stage IIIC ovarian carcinoma.

Case presentation

A 23-year-old female patient without significant past medical history was admitted in our Institute in March 2008, with mild abdominal pain and distended lower abdomen, symptoms that have increased in intensity over the last two months.

Physical examination revealed a distended abdomen by ascites and bulky pelvic masses. The rectal and pelvic examinations revealed tumors in the Douglas cul-de-sac. Except for these findings and emaciation, the physical examination was normal.

The abdominal ultrasound revealed a solid, lobulated, non-homogeneous, low vascularized, 16 cm tumor of the right ovary; it also described other confluent tumor nodules, with uterine compression, enlarged internal iliac lymph nodes and ascites. The left ovary was 3.2/5 cm and had the same tumor aspect. A few solid lesions, with the maximum diameter of around 2 cm, were described on the surface of liver segment 5.

Abdominal and pelvic CT examination showed a bulky (14/8.5 cm), lobulated, pelvic mass, composed of multiple tumor enhancing nodules located around the uterus, in contact with the parametria (Figure 1), ascites, few solid nodules located in the left side of the abdomen, with the same structure as the pelvic mass and a hepatic heterogeneous macronodule (3/2/4 cm), superficially located in segment 5 (Figure 2).

The liver presented a slight hypertrophy of the left lobe, with homogeneous structure before and after intravenous contrast administration.

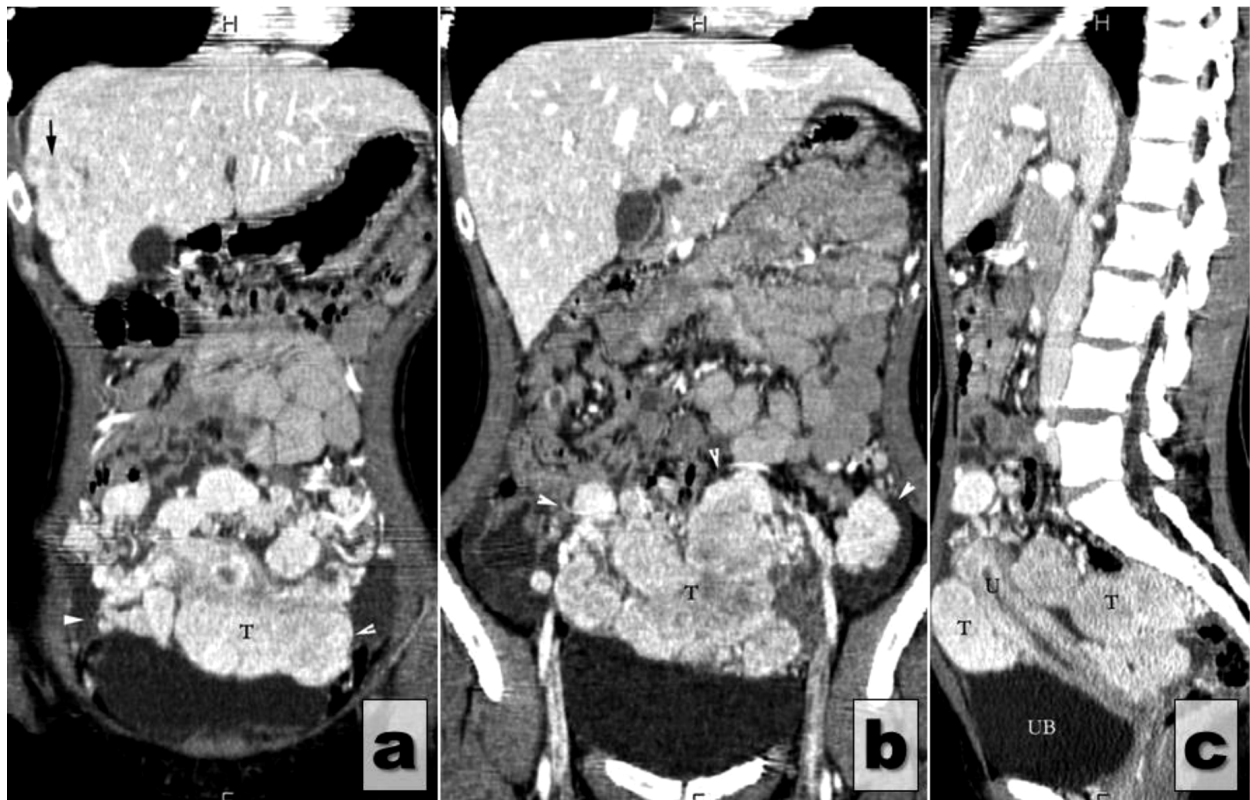


Figure 1 – Non-enhanced and enhanced CT examination of the abdomen and pelvis in coronal (a and b) and sagittal (c) plane reconstructions: large retro-/para-/pre-uterine pelvic mass (T) composed of multiple solid and enhancing tumor nodules (arrowheads), ascites, left peritoneal tumor nodule and liver mass located in segment 5 (arrow).

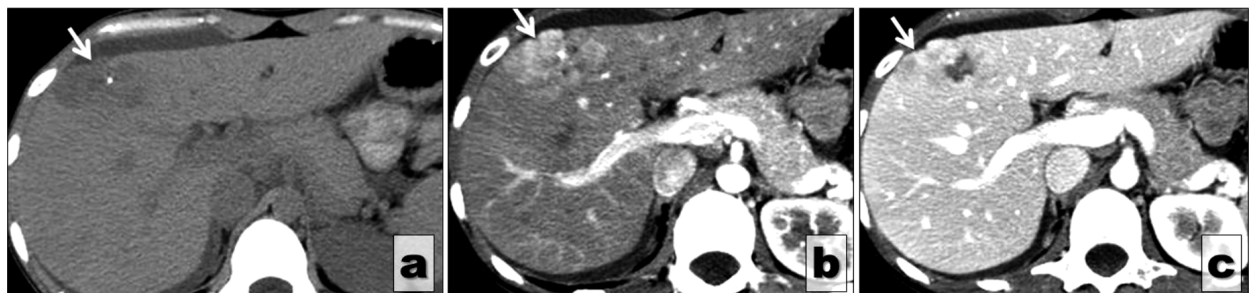


Figure 2 – Non-enhanced (a) and enhanced CT evaluation of the liver in arterial (a) and portal venous phase (b): the liver mass has a lobulated contour, a small central calcification, low attenuation on non-enhanced CT scans and a heterogeneous appearance after contrast administration with hyper attenuation in arterial phase and wash out in portal venous phase (arrow).

The initial diagnosis was stage IIIC ovarian carcinoma (we considered that the superficially located small liver tumor was just another peritoneal seeding). To exclude carcinomatosis due to a possible digestive primary tumor, upper and lower gastrointestinal (GI) tract endoscopies were performed, with normal results.

The only modified laboratory result was a mild increase of AFP – 23 ng/mL (normal levels – 9 ng/mL). Serum CA-125 levels were normal and the hepatic viral markers for B or C virus infection were negative.

Surgery was performed on 27.03.2008 and a peculiar aspect, not characteristic of ovarian carcinoma, was found. After evacuation of ascites, multiple round tumors of various sizes were visible at the level of the ovaries and the greater omentum (Figure 3a). Rare micronodules were found on the parietal peritoneum and the appendix. Intraoperative exploration also confirmed the small superficial hepatic tumor located in segment 5. Frozen sections of the tumors

showed a moderately differentiated G2 trabecular and alveolar adenocarcinoma. A complex R0 resection was performed: total hysterectomy with bilateral oophorectomy, total omentectomy, pelvic peritonectomy, segment 5 tumor-ectomy and appendectomy (Figure 3, b and c).

After electrofulguration of the peritoneal micronodules, intraperitoneal chemotherapy with 50 mg of Cisplatin was carried out.

The postoperative evolution was uneventful and the patient was discharged on the 9th postoperative day.

Histological examination of the tumors revealed, in the liver, a malignant microtrabecular/pseudoglandular proliferation consisting of polygonal cells with granular eosinophilic cytoplasm and prominent nuclei, placed in a dense, lamellar collagen stroma (Figure 4a) and, in the ovary, a dense lamellar collagen stroma harboring a malignant microtrabecular and pseudoglandular proliferation of polygonal malignant cells (Figure 4b).

The lesions were consistent with the diagnosis of moderately differentiated fibrolamellar hepatocellular carcinoma (Edmondson/Steiner II/III) with ovarian and peritoneal metastases.

Immunohistochemical examination of the specimens confirmed the diagnosis by showing cytokeratin (CK) 7

cytoplasmic positivity in many tumor cells, positivity for CK 8/18 in a few dispersed tumor cells, faint AFP positivity in tumor cells (Figure 5, a–c), zonal positivity for epithelial membrane antigen (EMA), diffuse positivity for carcinoembryonic antigen (CEA); 20 to 30% positivity for Ki67.

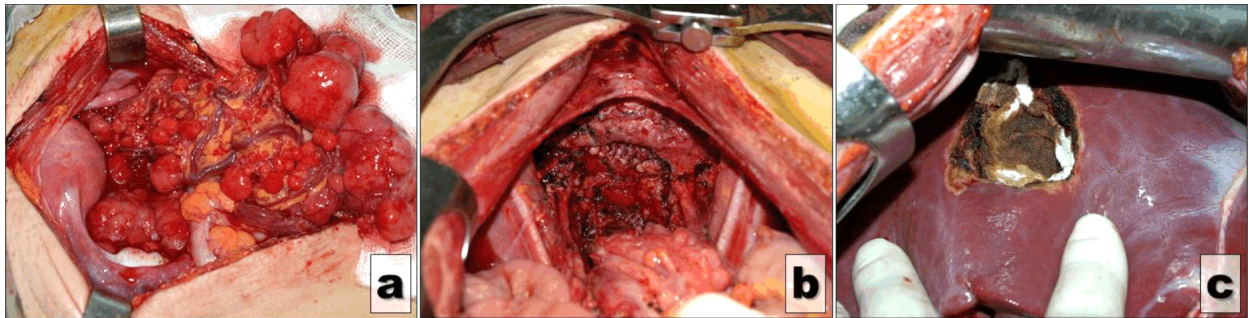


Figure 3 – Intraoperative aspects: (a) Multiple tumors developed at the level of the greater omentum and ovaries; (b) The pelvis after extensive resection of peritoneum, total hysterectomy and bilateral oophorectomy; (c) The liver following resection of the tumor located in segment 5.

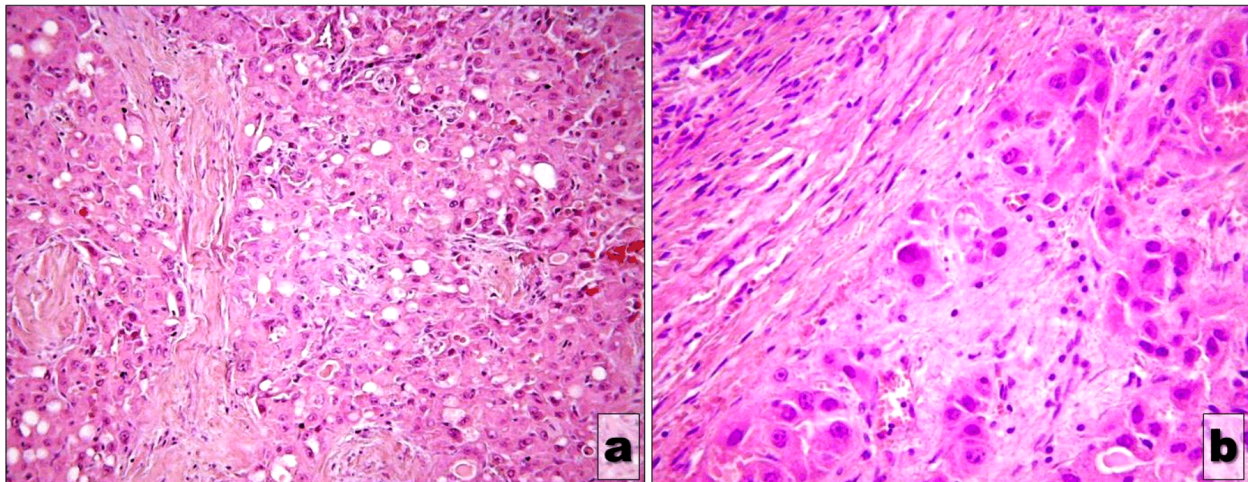


Figure 4 – (a) Histological aspect of liver tumor; (b) Histological aspect of the ovary. HE staining: (a) ×100; (b) ×200.

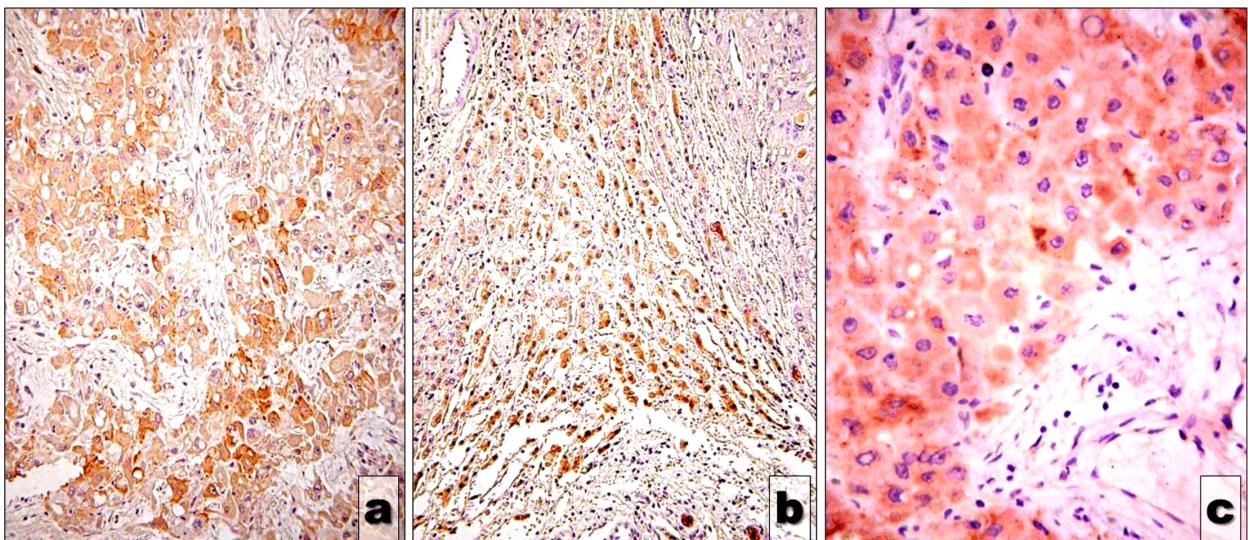


Figure 5 – Immunohistochemical examination: (a) CK 7 cytoplasmic positivity of variable intensity in many tumor cells (×100); (b) Faint CK 8/18 positivity in rare dispersed tumor cells (×40); (c) Faint AFP positivity in tumor cells (×200).

The patient underwent adjuvant chemotherapy (six cycles of Cisplatin and 5-Fluorouracil) and oncological follow-up in the Center of Gastroenterology and Hepatology, “Fundeni” Clinical Institute, Bucharest, Romania.

All postoperative follow-ups, including magnetic resonance imaging (MRI) and tumor markers, showed no signs of recurrence until May 2010, when MRI detected multiple peritoneal nodules. The patient underwent resection

of the recurrent tumors (bilateral paracolic, mesenteric, ileocolic and at the level of the round ligament of the liver) and intraoperative chemotherapy with Cisplatin. The histological examination of the resected specimens revealed once again aspects consistent with FLC: epithelial tumor proliferation with alveolar and trabecular disposition

placed in a dense collagen stroma; polygonal cells with abundant eosinophilic cytoplasm, enlarged round tachy-chromatic nuclei with atypical mitoses (6–10/10 high power fields – HPFs).

The extended immunochemical panel used (Table 1) pleaded for the diagnosis of relapsed FLC.

Table 1 – Immunochemical study of the resected recurrence

Marker	Positive on tumor cells' membrane	Positive in tumor cells	Focally positive in tumor cells	Negative
CK 7	Yes			
AFP	Yes			
WT-1	Yes			
CD10	Yes			
CK 5/6		Yes		
CK 8/18		Yes		
Bcl-2		Yes		
ER		Yes		
TTF-1		Yes		
CEA			Yes	
EMA			Yes	
CD15			Yes	
CK 20				Yes
Collagen IV				Yes
Fibronectin	Positive at the level of sinusoids			

WT: Wilms tumor; Bcl: B-cell lymphoma; ER: Estrogen receptor; TTF: Thyroid transcription factor.

Despite postoperative chemotherapy with Sorafenib, other peritoneal recurrences intervened and were resected in November 2010 and in March 2012. The patient died in April 2013 by generalized disease.

Discussion

In recent years, FLC has been considered a distinct clinical entity *vs.* HCC with respect to its epidemiology, etiology, and prognosis. Moreover, FLC shows no evidence of chromosomal changes, gene dysregulation or mutations as with typical HCC, including AFP, TP53 mutations, and β -catenin mutations [14, 15].

Although rare, ovarian metastases from primary liver tumors are described in literature. There are nine reported cases with ovarian metastases from HCC [16–23], one case of metastatic hepatoblastoma in an adult [24] and 19 from cholangiocarcinoma [25–28]. Only two cases of ovarian metastases from FLC have been described to date. Bilbao *et al.* [11] and Montero *et al.* [12] have reported the case of a 45-year-old female patient with a large segment 2–3 FLC, peritoneal and bilateral ovarian metastases; following a complex resection and postoperative chemotherapy, the patient was alive 24 months postoperatively, with recurrence. The second case was published in 2012 by Benito *et al.* [13] – a 26-year-old female patient with a liver segment 2–3 tumor with right ovarian and omental metastases; the primary resection of the metastases was followed by a liver tumor resection. She underwent chemotherapy with Sunitinib. The patient was free of disease at 12 months.

In our patient, the main complaint was the enlargement of the lower abdomen. Pelvic and abdominal masses were found during clinical examination, suggestive for ovarian carcinoma. Pain, a common symptom of FLC, which is usually well tolerated due to the age of the patients (between 10 and 30 years), was absent in this case.

In most cases of FLC, the AFP levels are normal (even in patients with associated FLC-HCC [8]). Rare ovarian tumors – the yolk sac tumor (also called endodermal sinus tumor), the hepatoid carcinoma of the ovary and other epithelial ovarian tumors produce AFP, thus making difficult the differential diagnosis between these tumors and HCC metastases to the ovaries. Plasma neurotensin levels [29] and vitamin B₁₂ binding capacity (tumor markers significantly increased in FLC) [30, 31] were not determined preoperatively in our patient, since there was no suspicion of FLC.

More than 80% of the FLCs have a lobulated surface on CT examination. Small central calcifications are seen in 35–68% of the tumors. Most the FLCs have a heterogeneous aspect, with areas of low attenuation on non-enhanced CT scans. During the hepatic arterial phase enhancement, these lesions are hyper-attenuating in 80% of cases. A central scar (stellate or amorphous) is seen in 20–71% of cases [32]. Consequently, the most frequent differential diagnosis is between FLC and focal nodular hyperplasia (FNH). There are imagistic criteria differentiating the two entities: calcifications are frequently seen in FLC on CT and the central scar of FLC is visualized as an area of low intensity on T2-weighted MRI [33, 34]. Some authors have suggested that FLC could be the malignant variant of FNH [35].

None of the imagistic criteria for diagnosis of FLC were present in our case. Moreover, due to the presence of the large abdominal masses, the small superficial liver lesion was considered another secondary seeding (also, during surgery it was easily resected/enucleated, not having the typical macroscopic characteristics of a primary malignant liver tumor). Instead of a large liver tumor with invasion of adjacent structures there was a relatively small, superficial liver tumor; the peritoneal and ovarian masses being more large than the liver tumor.

An aggressive surgical liver resection and resection of invaded organs should be attempted in most cases of FLC. Lymphadenectomy is also recommended since nearly half of the patients develop lymph node or distant metastases [7]. The resectability rate is around 70% [8]. Despite small number case series [36–38], it seems that living donor liver transplantation could evolve into a potentially better alternative to resection in patients with large FLCs.

Histological diagnosis should differentiate between HCC, FLC and ovarian hepatoid carcinoma. While the aspect of FLC is quite characteristic, immunohistochemical staining is sometimes required to differentiate metastatic HCC/FLC from ovarian yolk sac tumor with hepatoid differentiation. Immunoreactivity for CK 7 is characteristic for FLC and is negative in hepatoid ovarian tumors.

The prognosis of fibrolamellar carcinoma was considered to be better than HCC but a recent study of Kakar *et al.* [7] showed that prognosis of FLC is similar to conventional HCC without cirrhosis. Among non-metastatic cases, the prognosis is better in FLC and HCC without cirrhosis (45% survival at five years) compared to hepatocellular carcinoma with cirrhosis (27%). The better outcome in FLC appears to be due to the absence of cirrhosis rather than to its distinct clinical pathological features [7].

Prognosis is better in patients who undergo resection with negative margins [14], tumor stage [36], and age over 23 [39].

Late recurrences are common and occur in nearly all cases but early detection of relapse combined with multimodality therapy results in prolonged survival [40]. Since there are no other effective treatment options, repeat resections for recurrence should be considered.

✉ Conclusions

Amongst FLC patients, a subset in which the tumor has a peculiar biological behavior, like the case we presented in this paper, can be individualized. The superficial location of the liver tumor, which made possible early peritoneal and ovarian seeding, could be the explanation of this rare FLC presentation. Tailored combined/multimodal therapy applied to this peculiar case allowed five-year survival for a stage 4 FLC patient.

Conflict of interests

The authors declare that they have no conflict of interests.

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