Bilateral Adnexal Masses in a Young Female: Rare Presentation of Hepatocellular Carcinoma With Review of the Literature

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Ovaries are a common niche for metastasis. Metastatic malignancies account for 5–30% of all ovarian malignancies. Hepatocellular carcinoma (HCC) is one of the rare malignancies to metastasize to the ovaries. Of all the variants of HCC, fibrolamellar HCC (FLHCC) variant is extremely uncommon and accounts for around 1% of all HCC cases. FLHCC metastasizing to ovaries, at presentation, is an exceptional occurrence. We present a case of a young female who presented with bilateral adnexal masses and was diagnosed as metastatic FLHCC on histopathological examination and confirmed by immunohistochemistry. In addition, a thorough literature review highlighting the previously reported cases is also presented. (J CLIN EXP HEPATOL 2020;10:636–640)

Ovaries are a common site of metastasis from other primary malignancies.¹ Most common primary sites include stomach, appendix, colon, breast, small intestine, rectum, gallbladder, urinary bladder, and the kidneys.² Hepatocellular carcinoma (HCC) is one of the rare malignancies to metastasize to the ovaries with less than 15 cases reported in the literature, till date.^{3–5} Of all the variants of HCC, fibrolamellar HCC (FLHCC) type is extremely rare, accounting for 1% of all HCC cases. FLHCC is a distinct variant of HCC which differs from the conventional HCC with respect to epidemiology, etiopathogenesis and genetics.⁶ Older studies have reported a better prognosis of FLHCC as compared with the conventional HCC, however, more recent studies have undoubtedly recognized that the survival benefit in FLHCC is not significantly superior to that in HCC cases without any coexisting cirrhosis.⁷ These

are locally aggressive neoplasms and also have a high propensity to metastasize. Peritoneal and lymph nodal metastases are more common with FLHCC than with the conventional HCC.⁸ However, metastasis to ovaries is an exceptional occurrence with only 3 such cases reported previously.^{9–12} Herein, we present a case of a young female who presented with bilateral adnexal masses and on subsequent histopathological examination was diagnosed as having fibrolamellar variant of HCC, metastatic to both the ovaries.

CASE REPORT

A 35-year-old woman presented with pain in right iliac fossa with abdominal distension for the last one month. Pain was radiating to anogenital region. Pain was intermittent and dull in nature and was associated with nausea, vomiting, and dyspepsia. On physical examination, patient was emaciated, and systemic examination revealed a distended, nontender abdomen. Per speculum examination revealed normal cervix and vagina. Per vaginum examination revealed a mass in right cervical region measuring 4 × 4 cm with smooth surface and firm consistency. Left adnexa and bilateral fornices were free. On per rectal examination, rectal mucosa was free, and a mass was felt in pouch of Douglas. Her liver function tests revealed elevation of alkaline phosphatase (131.5 U/L; normal range – 30–120 U/L) and aminotransferases (ALT: 116.6 U/L; normal range – 0–35 U/L, AST: 90.71 U/L; normal range – 0–38). CEA, CA19-9 and alpha-fetoprotein (AFP) levels were within normal limits. CA-125 was only mildly increased (52 IU/ml; normal range – 0–35 IU/ml). She

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Abbreviations: HCC: Hepatocellular carcinoma; FLHCC: Fibrolamellar hepatocellular carcinoma; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CEA: Carcinoembryonic antigen; CA19-9: Cancer antigen 19-9; CA-125: Cancer antigen-125; HIV: Human Immunodeficiency virus; HCV: Hepatitis C virus; HBsAg: Hepatitis B surface antigen; CK7: Cytokeratin-7; HepPar-1: Hepatocyte paraffin antigen-1; CD68: Cluster differentiation 68; PAX8: Paired box gene 8; AFP: Alpha-fetoprotein; CK19: Cytokeratin 19; CT: Computerized tomography

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Figure 1 a) Gross photograph showing normal sized uterus with attached left ovary and fallopian tube and separately lying enlarged right ovary with lobulated outer surface and fallopian tube and omentum with multinodular appearance; (b) Cut section showing solid lobulated appearance of the right ovary with solid tumor nodules in the omentum, the uterus is unremarkable grossly.

was nonreactive for human immunodeficiency virus, hepatitis C virus, and hepatitis B surface antigen serology. Abdominal ultrasound revealed an ill-defined hypoechoic lesion measuring 5.9×3 cm in segment VIII of the liver. Magnetic resonance imaging of the pelvis revealed a large, solid, lobulated, nonhomogeneous mass, arising from right ovary, measuring $7 \times 7 \times 6$ cm. The left ovary was bulky, measuring $4.5 \times 3 \times 2$ cm, solid in appearance, and lobulated in outline. In addition, there were multiple enlarged lymph nodes in right external iliac region, largest measuring 1.5×1.5 cm. A provisional clinical diagnosis of primary ovarian malignancy with liver metastasis was made.

Patient underwent total abdominal hysterectomy with omentectomy and biopsy from the mass adherent to the liver. Intraoperative findings revealed 500 ml of ascites, bilateral tubo-ovarian masses, and multiple peritoneal deposits. Gallbladder was not identified distinctly, and an irregular mass was seen in the gallbladder fossa, adherent to the liver.

Grossly, right ovary measured $7 \times 6 \times 4$ cm with attached fallopian tube measuring 4 cm in length. Right ovarian surface was bosselated and showed multiple tumor deposits. Cut surface showed solid yellowish to gray-white areas. Left ovary measured $4 \times 2.5 \times 2.5$ cm with attached fallopian tube measuring 4 cm in length. Cut surface showed similar yellowish-white areas. Both the fallopian tubes were grossly unremarkable. Omentum showed multiple large tumor deposits, largest measuring $5 \times 4 \times 4$ cm (Figure 1). Biopsy from the mass adherent to liver measured $1 \times 1 \times 0.5$ cm. Histopathological examination of both ovaries revealed a tumor arranged predominantly in nests, trabeculae, cords and focally in a pseudoglandular pattern. The tumor cell nests were separated by fibrotic bands which were better highlighted on Masson trichrome stain. The individual tumor cells were large, polygonal, with mild to moderate nuclear pleomorphism, round to oval nuclei, vesicular chromatin, prominent macronucleoli and moderate to abundant amount of eosinophilic cyto-

plasm. Intracytoplasmic and canalicular brownish pigment was also noted which was confirmed to be bile using Fouchet's stain (Figure 2). Sections from the omentum showed metastatic deposits composed of tumor cells with similar morphology. The biopsy from the mass adherent to the liver also showed tumor with similar morphology (Figure 3). Sections from the cervix, bilateral fallopian tubes and endomyometrium were free of tumor.

Immunohistochemistry was also performed which confirmed the diagnosis of FLHCC and showed strong diffuse membranocyttoplasmic positivity for cytokeratin-7 (CK7), strong diffuse granular, cytoplasmic positivity for hepatocyte paraffin antigen-1 (HepPar-1) and granular, cytoplasmic positivity for CD68. The tumor cells were negative for PAX8, AFP, and CK19 (Figure 4). Based on the histopathological and immunohistochemical findings, a diagnosis of fibrolamellar variant of HCC, metastatic to both the ovaries and omentum was rendered.

After the diagnosis and recovery from surgery, our patient was started on sorafenib in a dose of 400 mg/day. Although, surgical resection or transplantation is the standard of care for fibrolamellar carcinoma for eligible patients, our patient has metastatic disease with extrahepatic spread. Hence she underwent one session of locoregional therapy by transarterial chemoembolization (TACE).⁶ Under fluoroscopic guidance, selective cannulation of artery supplying the tumor was performed, and 50 mg of foamed doxorubicin was injected into the vessel followed by gel-foam embolization. There were no immediate postprocedure complications, and the lesion showed good lipoidal uptake. Post-TACE CT revealed complete lipiodol uptake in the largest HCC lesion in segment VIII with no residual arterial enhancement. The other nodules are too small to be treated, by ablative modalities, at present. She is planned for close follow-up. After TACE, patient was continued on sorafenib 400 mg/day and is on regular outpatient follow-up. She is a candidate for immunotherapy with nivolumab or pembrolizumab, which will be assessed on follow-up.

Figure 2 a) Representative sections from both the ovaries showing tumor cells arranged in nests, cords, and trabeculae (H&E; 2×); (b) Higher magnification showing the arrangement of tumor cells as cords and trabeculae separated by fibrous bands (H&E; 10×); (c) Higher magnification showing the large polygonal tumor cells with large vesicular nuclei, prominent macronucleoli and abundant amount of eosinophilic cytoplasm (H&E; 40×); (d) Tumor cells with intracytoplasmic bile (H&E; 40×); (e) Fouchet's stain highlighting the bile pigment in green color (Fouchet's stain; 40×); (f) Masson trichrome stain highlighting the fibrous tissue surrounding the tumor cells in green (Masson trichrome; 10×).

DISCUSSION

Ovaries are one of the common sites for metastasis from a variety of primary malignancies, most common being from the gastrointestinal tract and the breast. HCC, especially the fibrolamellar variant of HCC is one of the rarest malignancies to metastasize to the ovaries. FLHCC has been recognized as a distinct variant, which unlike conventional HCC arises in noncirrhotic background and affects younger individuals. In addition, AFP levels are normal in FLHCC in contrast to HCC, which is characterized by elevated AFP levels. Recently, FLHCC has been found to be associated with a novel chimeric transcript DNAJB1-PRKACA.¹³

Clinically, the patients usually present with nonspecific symptoms including abdominal pain, weight loss, and

anorexia. Most of the times, liver function tests are normal or mildly elevated and therefore, many of these patients present in advanced stages, with large tumors invading adjacent structures. Traditionally, it has been considered to be less aggressive than conventional HCC, however, more recently it has been recognized that the prognosis is comparable with the conventional HCC arising in non-cirrhotic background. Surgical resectability has been identified as the most important prognostic determinant in FLHCC. Ultrasonographically, FLHCC has nonspecific features and is most often seen as well-defined mass of variable echogenicity and may mimic focal nodular hyperplasia. Multiphasic computerized tomography using a liver protocol and dynamic contrast enhanced magnetic resonance imaging are preferred modalities for further characterization of such lesions.

Figure 3 a: Section from the omental nodule showing tumor cells with similar morphology infiltrating the adipose tissue (H&E; 20×); (b) Section from the biopsy from the mass over the surface of liver showing similar tumor cells (H&E; 20×).

Figure 4 a) Immunohistochemistry for CK7 showing strong diffuse membranocyttoplasmic positivity in the tumor cells (CK7; 10×); (b) Immunohistochemistry for HepPar1 showing strong diffuse cytoplasmic positivity in the tumor cells (HepPar1; 20×); (c) Immunohistochemistry for CD68 showing granular cytoplasmic positivity in the tumor cells (CD68; 20×); (d) Immunohistochemistry for CK19 is negative in the tumor cells (CK19; 20×); (e) Immunohistochemistry for PAX8 is negative in the tumor cells (PAX8; 20×); (f) Immunohistochemistry for alpha-fetoprotein is negative in the tumor cells (AFP; 20×).

Table 1 Review of the Literature Showing All the Reported Cases of Fibrolamellar Hepatocellular Carcinoma Metastatic to Ovaries.

Author	Age	Clinical history	Radiology	AFP levels	Site	IHC	Diagnosis
Montero A and Bilbao I <i>et al</i> ^{9,10}	45	Presented as Krukenberg tumor	MRI showed 2 large ovarian masses, measuring 11 and 12 cm and a large tumor in the left hepatic lobule	Normal	Bilateral ovaries and omentum	HepPar1 and CK7 positive, AFP negative	Metastatic Fibrolamellar HCC
Benito V <i>et al</i> ¹¹	26	Known case of Fibrolamellar HCC	CT showed a 14 and 12 cm ovarian tumor and an 8 cm liver lesion affecting the II – III segment	Normal	Bilateral ovaries and omentum	Not done	Metastatic Fibrolamellar HCC
Ciurea SH <i>et al</i> ¹²	23	Presented as Krukenberg tumor	CT examination showed a bulky (14 × 8.5 cm), lobulated, pelvic mass, and a heterogeneous hepatic macronodule (3 × 2 × 4 cm), superficially located in segment V	Mild increase	Bilateral ovaries and omentum	CK7, CK8/18, AFP positive	Metastatic Fibrolamellar HCC
Present case	35	Presented as Krukenberg tumor	MRI pelvis revealed large, solid, lobulated, mass measuring 7 × 7 × 6 cm and arising from right ovary. The left ovary was also bulky, measuring 4.5 × 3 × 2 cm, solid in appearance and lobulated in outline. There was also an ill-defined hypoechoic lesion measuring 5.9 × 3 cm in segment VIII of the liver	Normal	Bilateral ovaries and omentum	HepPar1, CK7, CD68 positive, AFP negative	Metastatic Fibrolamellar HCC

*AFP: alpha-fetoprotein; IHC: immunohistochemistry; CT: computerized tomography; MRI: magnetic resonance imaging.

A definite diagnosis can be established only by histopathological examination followed by immunohistochemistry. Microscopically, it is characterized by the presence of nodules and sheets of large polygonal cells, with distinct cell borders, large round nuclei, vesicular chromatin, prominent macronucleoli, and abundant densely eosinophilic cytoplasm, with some cells showing characteristic intracytoplasmic pale bodies and hyaline bodies. Surrounding the tumor cells is the dense fibrous stroma, most often arranged as parallel lamellae.⁸ Immunohistochemically, FLHCC shows strong positivity for cytokeratin-7 (CK7), CD68 and HepPar-1. Both CK7 and CD68 are believed to be reliable markers for differentiating FLHCC from other hepatoid mimics. Yet another important differential that needs to be considered is primary ovarian hepatoid carcinoma, especially in cases with ovarian involvement, as in the present case. CK 7 positivity is peculiar for FLHCC and is not seen in primary hepatoid ovarian carcinoma.

To the best of our knowledge, till date, only three cases of FLHCC metastatic to the ovaries, have been reported in the world literature [Table 1].^{9–12} Two of these cases presented as Krukenberg tumor. Bilbao *et al* and Montero *et al* have reported the case of a 45-year-old female patient with a large FLHCC in left hepatic lobule with peritoneal and bilateral ovarian metastases, after a complex resection and postoperative chemotherapy. However, the patient died after 2 years.^{9,10} The second case was of a 26-year-old female patient with a liver tumor, right ovarian, and omental metastases; wherein the primary resection of the metastases was followed by a liver tumor resection.¹¹ The third case was of a 23-year-old female with a pelvic mass and a heterogeneous hepatic macronodule located superficially in segment V of liver. This patient had mild increase in AFP and focal positivity for AFP on immunohistochemistry. She underwent chemotherapy with Sorafenib, however died after 4 years due to disease dissemination.¹² Our patient is being treated as metastatic HCC, after one successful TACE with target lesion showing complete remission and is planned for immunotherapy on follow-up.

To summarize, although metastasis of FLHCC to the ovaries is an extremely rare phenomenon, clinicians, as well as the pathologists need to be well aware of this entity and the importance of immunohistochemistry in confirmation of the diagnosis. A high index of clinical suspicion in young patients with liver mass and a systematic radiologic work-up followed by tissue diagnosis is imperative for an early accurate diagnosis in such patients.

Authors contributions

GK: Writing the manuscript, collection and analysis of the data; **PG:** Conceptualization, drafting, editing and re-

viewing the manuscript; **PKS:** Clinical management of the patient, reviewing and editing the manuscript; **RM:** Clinical management of the patient, reviewing and editing the manuscript; **MP:** Clinical management of the patient, reviewing and editing the manuscript; **AR:** Management of the patient, reviewing and editing the manuscript

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CONFLICTS OF INTEREST

The author has none to declare.

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