Downstaging and resection after neoadjuvant therapy for fibrolamellar hepatocellular carcinoma

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Abstract

Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare malignant liver neoplasm, commonly observed in adolescents and young adults of both genders. The disease is more common in Caucasians and in patients without a prior history of liver disease. The best treatment option is a surgical resection associated with liver hilum lymph node dissection. However, there is no established systemic drug treatment for patients with locally advanced or metastatic disease. We report on a patient with advanced FLHCC, initially considered unresectable due to invasion of the right and the middle hepatic veins and circumferential involvement of the left hepatic vein. Following the treatment with gemcitabine-oxaliplatin systemic chemotherapy, the patient exhibited a significant tumor reduction. As a result, a complete resection was performed with an extended right hepatectomy associated with a partial resection of the inferior vena cava, a wedge resection in segment 2, and lymphadenectomy of the hepatic hilum. The case was unusual due to the significant tumor downstaging with gemcitabine-oxaliplatin, potentially enabling curative resection. More studies are needed to confirm the efficacy of the systemic drug treatment for FLHCC.

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Key words: Chemotherapy; Gemcitabine; Oxaliplatin; Hepatectomy; Hepatic veins; Fibrolamellar hepatocellular carcinoma

Core tip: Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare malignant liver neoplasm. The best treatment option is a surgical resection with liver hilum lymph node dissection. Currently there is no established systemic drug treatment for patients with locally advanced or metastatic disease. In this report, a patient with advanced FLHCC, initially considered unresectable due to vascular invasion, exhibited a significant tumor reduction following systemic chemotherapy with gemcitabine-oxaliplatin, allowing resection. This was an unusual case where gemcitabine-oxaliplatin treatment led to a significant tumor downstaging enabling curative resection. Additional studies are needed to confirm the efficacy of the systemic drug treatment for FLHCC.

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an uncommon primary liver neoplasm, representing 0.6%-8.6% of all hepatocellular carcinomas (HCC)\(^\text{[1]}\). It was first described in 1956 by Edmonson as a rare distinctive form of HCC\(^\text{[2]}\). In general, it is a vascular tumor with prominent fibrosis. Microscopically, FLHCC appears as a well-differentiated tumor comprised of large polygonal cells with large nuclei and nucleoli, as well as an abundant eosinophilic cytoplasm, arranged in lamellar bands of collagen fibers\(^\text{[3]}\). FLHCC most often affects adolescents and young adults of both genders, often Caucasian, and without a prior history of liver disease\(^\text{[1,4]}\). Liver function tests are typically normal or only mildly elevated. Commonly used HCC markers, such as alpha-fetoprotein, are of little help in diagnosing and monitoring disease progression in the majority of patients, as only a small proportion of patients (7%–11%) show elevation in alpha-fetoprotein levels\(^\text{[1,4]}\).

FLHCC is believed to more commonly metastasize to regional lymph nodes. The cornerstone for FLHCC treatment is a surgical resection associated with lymph node dissection\(^\text{[3,5]}\). Patients with advanced FLHCC represent a population in need of novel and effective treatments. Due to the lack of data on effective systemic drug treatments as well as the FLHCC patients’ paucity, it is difficult to conduct clinical trials\(^\text{[6]}\). The authors report an unusual case of a young patient, initially with an unresectable FLHCC, treated with gemcitabine-oxaliplatin (GEMOX), resulting in an excellent response and complete resection of the tumor.

**CASE REPORT**

A previously healthy 35-year-old Caucasian female complaining of abdominal pain, 3 kg weight loss, weakness, back pain, and a palpable mass in the right upper quadrant, was referred for evaluation. Physical examination disclosed a palpable hard mass 20 cm below the right costal margin. There were no signs of liver disease or other relevant findings. A computed tomography scan (Figure 1) showed a suggestive FLHCC mass (17 cm × 15 cm) affecting the right liver lobe. In addition, the mass affected segment 4b by obstructing the right portal branch, invading both the right and middle hepatic veins, circumferentially wrapping the left hepatic vein, and compressing the inferior vena cava. A lesion (ø 6.5 cm) in segment 2 displayed the same characteristics, as well as lymphadenopathy at the liver hilum up to 2.7 cm in size. Laboratory tests revealed elevated levels of alkaline phosphatase, gamma-glutamyl transpeptidase, and alpha-fetoprotein (44.395 ng/mL). Both hepatitis B and C serologies were negative. Colonoscopy and endoscopy results were normal. Percutaneous biopsy of the tumor confirmed FLHCC. The lesion was considered unresectable because of the extensive vascular involvement, especially of the hepatic veins; therefore, the patient was referred to an oncologist for a systemic drug treatment. Transplantation was eliminated due to the presence of the hilar lymph nodes (extra hepatic disease).

The patient received 100 mg of oxaliplatin and 1400 mg of gemcitabine (20 mg/kg) every two weeks during an 11-mo treatment period, with good tolerance. The staging intervals, scheduled every four months, included either a computed tomography scan or magnetic resonance imaging. After one year of treatment, magnetic resonance imaging showed significant tumor size reduction (the larger lesion size was 8.5 cm and the smaller 2.2 cm), decrease in contact with the left hepatic vein and inferior vena cava, disappearance of the lymphadenopathy, and hypertrophy of the left lateral segment of the liver (38% of total liver volume) (Figure 1). In addition, there was a significant decrease in alpha-fetoprotein levels to 45 ng/mL.

The patient was submitted to an extended right hepatectomy with partial resection of the inferior vena cava associated with a wedge resection in segment 2 and lymphadenectomy of the hepatic hilum. The procedure lasted 450 min with the patient receiving two units of packed red blood cells and staying in the intensive care unit for two days. The patient developed a postoperative biliary fistula, which was treated conservatively, with spontaneous closure after 28 d. Our patient was discharged on the 17\(^{th}\) postoperative day in a good clinical condition.

Histology examination confirmed FLHCC with microscopically free margins (R0 resection). The hepatic hilum lymph nodes were free of the disease. At discharge, the level of alpha-fetoprotein was within normal limits (4.7 ng/mL). The patient had no signs of the disease recurrence at the 14-mo follow-up.

**DISCUSSION**

The best treatment option for FLHCC is a resection with adequate lymph node dissection\(^\text{[3,4]}\). However, a resection is not always possible due to locally advanced disease. The best therapy for these patients has not been well established\(^\text{[1]}\). Several chemotherapy agents have been used for FLHCC treatment, including fluoropyrimidines, doxorubicin, cisplatin, oxaliplatin, gemcitabine, and irinotecan, as well as interferon, bevacizumab, and sorafenib in either combination regimens or separately\(^\text{[3,5]}\). Locoregional therapies, such as transarterial chemoembolization, radiofrequency ablation, external beam radiation, percutaneous ethanol injection, and hepatic arterial infusion of cisplatin, had disappointing results\(^\text{[3,8]}\). A study from the Fibrolamellar Carcinoma Consortium, which contained 99 patients diagnosed with FLHCC, showed that from the 73 patients who underwent surgery, 13% (10/73) received preoperative chemotherapy, external beam radiation, and/or transarterial chemoembolization. Twenty-one percent (20/99) were considered to have unresectable disease and 13 of them were treated with various combinations of systemic drug therapy with or without locoregional therapies. Chemotherapy agents used in the study included fluoropyrimidines, doxorubicin, cisplatin, oxaliplatin, gemcitabine, and irinotecan. However, a multivariate analysis showed a lack of surgery to be an independently poor overall survival predictor\(^\text{[10]}\). Kaseb et al\(^\text{[1]}\) studied 94 FLHCC patients and found tumor resection...
to be a factor positively associated with longer overall survival; 5-fluorouracil-interferon combination was the most frequently used systemic therapy.

HCC markers, such as alpha-fetoprotein, are of little help in diagnosing and monitoring disease progression in the majority of patients. This is mostly due to a small proportion of patients (7%-11%) showing elevated alpha-fetoprotein levels. Our patient probably belongs to this peculiar group since her initial levels of alpha-fetoprotein were high, and were lowered to normal levels following surgery.

Sorafenib is currently the standard treatment for advanced HCC. However, no systemic drug therapy had convincingly improved survival among patients with

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Figure 1 Abdominal computed tomography and magnetic resonance imaging of a 35-year-old Caucasian female, with no previous history of liver disease, showing a large mass in the upper right quadrant. A, B: Abdominal computed tomography (CT) before chemotherapy showing a large mass invading (17 cm × 15 cm) the right and the middle hepatic veins, and surrounding the left hepatic vein; C, D: Abdominal magnetic resonance imaging after gemcitabine-oxaliplatin chemotherapy showing significant reduction of the tumor size; E, F: Abdominal CT two weeks after surgery with hypertrophy of the left lateral segment of liver (liver remnant), and free and patent left branch of the portal vein and left hepatic vein; G, H: Late follow-up after 14 mo.
advanced HCC. There have been attempts to evaluate the efficacy of new drugs or combination treatments in clinical trials. Some of the examples of these trials include: (1) doxorubicin alone and/or with gemcitabine; (2) combination of cisplatin, doxorubicin, 5-fluorouracil, and alpha-interferon; and (3) combination of intrathecal, taxanes, gemcitabine, topotecan, and thymidine synthase inhibitors\[10\]. The GEMOX regimen appeared to be the most promising, based on a lack of renal and hepatic toxicity in cirrhotic patients, promising efficacy in the phase II trials for advanced HCC, and with possible extended benefit for Child B cirrhosis\[10,14\]. Louafi et al\[15\], studying 32 patients treated for advanced HCC, had two patients that underwent HCC curative resection after partial response to GEMOX. In a retrospective multivariate study, Zaanan et al\[16\] observed tumor responses in 204 patients with advanced HCC treated with GEMOX. In 10 patients, tumor response either permitted secondary surgical resection of residual tumors or orthotopic liver transplantation. Radiofrequency ablation was performed in one patient, transcatheter arterial chemoembolization in three patients, cyberknife treatment in one patient, and radioembolization in two patients. There was also a case report on a patient with metastatic HCC without liver disease with a complete response after 12 cycles of GEMOX\[17\].

There has been only one reported case of FLHCC with a complete response after GEMOX treatment. In this case, a young woman had a histologically proven metastatic lymph node relapse after resection of the primary tumor. GEMOX regimen lead to a complete response without relapse five years after chemotherapy discontinuation\[18\]. HCC patients have poor tolerance to systemic chemotherapy, mostly due to cirrhotic liver\[19\]. In most cases FLHCC patients do not have a prior history of liver disease\[20\]. This may explain the better tolerance to chemotherapy, hence leading to a better response, as is the case in our patient. In the present case, the chemotherapy regimen with GEMOX promoted FLHCC downstaging, potentially allowing for a curative treatment. However, more studies are needed to confirm GEMOX efficacy.

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