Successful Multimodal Treatment for Aggressive Metastatic and Recurrent Fibrolamellar Hepatocellular Carcinoma in a Child

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Summary: Fibrolamellar variant of hepatocellular carcinoma (FLHCC) does not have a favorable prognosis than conventional HCC, and there is no difference regarding the response to chemotherapy and the degree of surgical resectability. FLHCC commonly recurs after complete surgical resection, and there is a high rate of lymph node metastases. Herein, we report a 12-year-old girl with metastatic FLHCC with multiple recurrences aggressively treated with surgery, chemotherapy, and antiangiogenic agents. She is in complete remission after 4 years and 2 months after the diagnosis of metastatic FLHCC. The standard treatment of FLHCC is excision of the primary tumor and its metastases. Chemotherapy for FLHCC is controversial, and it has been suggested that cytoreductive chemotherapy was ineffective and adjuvant chemotherapy did not improve survival. Our patient with multiple recurrences was successfully treated with surgery, first-line chemotherapy with cisplatin and doxorubicin, second-line chemotherapy with 5-fluorouracil/interferon-α combination, and adjuvant antiangiogenic agents like cyclophosphamide and thalidomide. As FLHCC patients have no underlying liver disease, they can tolerate higher doses of chemotherapy compared with conventional HCC patients. We support the use of repeated aggressive surgery with adjuvant chemotherapy and antiangiogenic therapy, which provided complete remission in our patient with metastatic and recurrent FLHCC.

Key Words: fibrolamellar hepatocellular carcinoma, surgery, chemotherapy, antiangiogenic therapy, 5-fluorouracil, interferon-α

CASE REPORT

A 12-year-old girl was admitted to hospital with a weight loss of 5 kg in last 3 months, intermittent constipation, and fatigue. Physical examination revealed an enlarged liver of 4 cm and 6 cm in the midclavicular line and below the xiphoid process, respectively. Laboratory investigations were significant for a C-reactive protein level of 74.3 mg/dL, erythrocyte sedimentation rate of 85 mm/h, and hemoglobin level of 9.5 g/dL, with normal aspartate aminotransferase, alanine aminotransferase, prothrombin time, activated partial thromboplastin time, γ-fetoprotein, and β-human chorionic gonadotropin. Hepatitis B surface antigen was negative and Anti-HBs was 1771 IU/mL. Abdominal ultrasound and computed tomography (CT) showed mass lesions of 57 × 50 × 50 mm, 58 × 62 mm, and 60 × 56 mm in the fifth to sixth segments, adjacent to caudate lobe, and in the fourth segment of the liver, respectively, along with a 32 × 32 × 48 mm para-aortic lymphadenopathy. Thorax CT was normal. An 18F-FDG-PET CT scan showed enhanced metabolic activity in the mass lesions of the liver (SUVmax = 6.7) and in the para-aortic lymph nodes (SUVmax = 8.3) (Figs. 1A, B). Histopathologic examination of the tumor tissue obtained by USG-guided trucut biopsy from the liver mass revealed a tumor mass composed of wide trabeculas, which are made up of tumor cells with large eosinophilic granular cytoplasm and atypical hyperchromatic nuclei and infiltrated with fibrous irregular lamellar stromal areas. The patient was diagnosed as hepatocellular neoplasia (compatible with FLHCC) and treated with 4 cycles of chemotherapy with cisplatin and doxorubicin. There was a subsequent regression of the mass lesions in the liver after chemotherapy but the para-aortic lymph nodes continued to increase in size. Therefore, the patient underwent partial hepatic resection and intra-abdominal lymph node excision. Microscopically, lobulated tumoral liver mass measuring 6 cm in its greatest dimension had a cut surface of grayish-white fibrous texture in central portion and orange-tan color at the periphery. Microscopic examination of the resection material revealed almost the same histopathologic features as the needle biopsy (Figs. 2A–C). Therefore, diagnosis of pure FLHCC was determined. Surgical margins were free of tumor. There was no cirrhotic change in nontumoral liver parenchyme. Moreover, a metastatic lymph node was detected at the portal hilus of the liver (Fig. 2D).

Postoperative 18F-FDG-PET CT scan was completely normal and she received adjuvant antiangiogenic treatment with cyclophosphamide and thalidomide for 6 months. However, a mass lesion adjacent to right liver lobe and surrounding multiple lymph nodes were detected during a routine follow-up after 21 months of surgery. A second operation consisting of the removal of a tumor of 70 × 60 mm extending from the first resection area of the liver to
the superior of the pancreas and celiac lymph nodes was performed. Histopathologic examination revealed a tumoral mass of FLHCC showing hemorrhagic and focal necrotic areas, as well as diffuse angiolymphatic invasion. There was no residual tumor at the resection margins. Twenty-three metastatic lymph nodes were detected. Postoperative evaluation with abdominal magnetic resonance imaging (MRI) after 1 month showed again a recurrent mass of 4.5 × 2.5 × 2 cm and lymph nodes adjacent to the operation lodge (Fig. 1C). Treatment with 5-fluorouracil (5-FU, 200 mg/m²/d continuous infusion for 21 d) and interferon-α (IFN-α, 4 × 10⁶ U subcutaneously on days 1, 3, and 5 of each week) was administered for 4 cycles. The patient was hospitalized during 3 weeks for each course, as treatment cycles were repeated every 28 days, she had only 1 week off before the next course. The regimen was very well tolerated and no side effects other than fatigue and anorexia were observed. There was an extremely good response to 5-FU/IFN-α combination, and abdominal MRI showed no residual tumor and no other abnormalities other than minimal heterogeneity at the
resection margins of the liver, indicating a complete response (Fig. 1D). However, abdominal MRI after 3 months of follow-up showed multiple mesenteric lymph nodes with the biggest being 40 x 25 mm and 18F-FDG-PET CT scan demonstrated an increased metabolic activity of SUVmax 14.9. The patient underwent a third operation in which all intra-abdominal metastatic conglomerated lymph nodes were completely excised. Adjuvant antiangiogenic treatment with cyclophosphamide and thalidomide were again started, and the patient was disease-free after 11 months of the last surgery (4 y and 2 mo after the diagnosis of the metastatic FLHCC).

**DISCUSSION**

FLHCC differs from HCC with regard to patient demographics, underlying risk factors, and tumor markers. Pathologic features including the presence of tumor cells with a deeply eosinophilic cytoplasm, and macronucleoli surrounded by abundant fibrous bands are essential in the diagnosis of FLHCC. FDG-PET proved to be a useful investigation for defining extrahepatic disease. FLHCC frequently present with an advanced stage with metastases to lymph nodes, peritoneum, and distant organs. The lymph nodes are commonly involved in FLHCC and also in recurrent disease, in contrast to the conventional HCC in which there is predilection for hepatic recurrences. Although the reason for the high rate of lymph node metastases with FLHCC is unknown, it was suggested that the cirrhotic process may inhibit lymphatic outflow and subsequent lymphatic metastases in conventional HCC.

The standard treatment of FLHCC is surgery with lymphadenectomy, as there is a high rate of lymph node metastasis and lymph nodes are common sites of first disease recurrence. Although FLHCC is often diagnosed at a stage that would not allow surgery, aggressive resection of the primary tumor and recurrences is generally recommended and may result in long-term survival. Stipa and colleagues reported a 5-year survival of 76% with surgery alone and considered complete excision as the best treatment for FLHCC. They suggested that the resectability rate in FLHCC may be higher given that tumors are usually well defined and occur in young patients with healthy livers.

Chemotherapy for conventional HCC and FLHCC is controversial. It has been suggested that cytoreductive chemotherapy was ineffective and adjuvant chemotherapy did not improve survival. Childhood Liver Tumour Strategy Group (SIOPEL) recommends preoperative chemotherapy with alternating cycles of cisplatin and carboplatin/doxorubicin after diagnostic biopsy followed by delayed surgical excision ± adjuvant chemotherapy with the same agents. In SIOPEL-2 and SIOPEL-3 trials including 62
patients with either pathology-proven well-defined FLHCC (n = 24) and conventional HCC (n = 38), the rate of response to chemotherapy was 31% and 55%, respectively. In the light of these results, chemotherapy for conventional HCC and FLHCC is unclear: In this study, the higher complete resection rate observed in the FLHCC group was thought to be correlated with the higher survival rate of these patients at early follow-up. However, late recurrence caused a delayed decline in survival in this group compared with the HCC. The authors support a radical surgical approach at the earliest opportunity in FLHCC because of tendency to extra-abdominal metastases, resistance to chemotherapy, and the relatively less aggressive behavior of this tumor.4

As FLH usually presents with large volume liver disease or metastases, treatment modalities such as transarterial chemoembolization or radiofrequency ablation have a limited role.3,10

Despite an indolent course, FLHCC frequently recurs after complete resection. Repeated surgery or orthotopic liver transplantation is recommended at recurrence, given the lack of proven effective adjuvant systemic treatment strategies.5,8–11 However, surgery only seems to be inadequate to control metastatic FLHCC and although the efficacy is questionable, neoadjuvant and adjuvant chemotherapy may be useful to reduce the tumor size. Shrinkage of the tumor with effective chemotherapy regimens will also increase the percentage of patients amenable to complete resection. The most commonly used agents for HCC in children are platin derivates and doxorubicin (PLADO regimen). Alternative treatment approaches were mostly used in adults. There are case reports in which gemcitabine-oxaliplatin (GEMOX regimen) resulted in complete remission.2,13 Also, 5-FU/IFN-α combination was used in adults systemically for resectable HCC in postoperative adjuvant setting or as part of multimodal treatment. Patt et al.,14 who used this combination in 8 patients with FLHCC, obtained a significant antitumor response inducing adequate tumor shrinkage in a few patients to allow surgical resection. Recently, Kaseb et al.15 published a series of 27 patients treated with 5-FU/IFN-α combination and reported only 2 patients with complete response and 6 patients with partial response, suggesting potential benefit from 5-FU/IFN-α combination in the neoadjuvant, adjuvant, and metastatic setting. Uchino et al.16 found a disease-control rate of 32.7% with the combination of systemic intravenous 5-FU and subcutaneous IFN in a large series of 223 patients with advanced hepatocellular carcinoma. Although the effectiveness of 5-FU/IFN-α combination is not proven in children with FLHCC, our patient having multiple recurrences had no other chance other than systemic control of the disease. We preferred systemic 5-FU simply because our patient had metastatic disease and intra-arterial administration is removed by the liver in the first pass.15 In contrast, as FLHCC patients have no underlying liver disease, they can tolerate higher doses of chemotherapy compared with conventional HCC patients. The combination of IFN-α and 5-FU has both direct growth inhibitory effects on endothelial cells and antiangiogenic effects through regulation of angiogenic factors VEGF, Ang1, and Ang2 released from HCC cells.17 Further, IFN-α and 5-FU combination synergistically inhibits the growth of Fas-negative HCC cells, arrest cell-cycle progression, and induce apoptosis.18 Local treatment modalities such as transarterial chemoembolization or radiofrequency ablation were not suitable for our patient who needed systemic control of the disease. Moreover, extrahepatic intra-abdominal metastasis at diagnosis and recurrences excluded the possibility to perform orthotopic liver transplantation in our case. Fortunately, front-line chemotherapy provided shrinkage of the tumor allowing delayed resection, inoperable relapsed disease completely regressed after 5-FU/IFN, and subsequent recurrence was amenable to complete excision in our patient. Thus, we strongly support the use of aggressive surgery with multiple resections and chemotherapy in children with relapsed FLHCC, rather than moving to palliative care or experimental treatments.10,12,19

Finally, Sorafenib, an oral multikinase inhibitor, is the new standard for the first-line treatment of advanced HCC in adults.20 It has been shown to improve survival in patients with HCC but the objective response rate is low and it is restricted to patients with compensated cirrhosis (Child-Pugh A). However, as FLHCC is not usually associated with cirrhosis and young patients respond well to chemotherapy, sorafenib is not the treatment of choice in childhood.10,12,13 Sorafenib was also not available in our patient because of legal restrictions and we administered adjuvant antiangiogenic treatment with cyclophosphamide and thalidomide to eradicate microscopic tumor foci and prevent recurrent disease.

In conclusion, our patient with metastatic FLHCC has benefited from 5-FU/IFN-α combination and achieved a complete response. We suggest the use of 5-FU/IFN-α not in a routine setting but especially in children with inoperable FLHCC. Although 5-FU/IFN-α combination requires hospitalization for 3 weeks with continuous infusion treatment, it can be well tolerated in FLHCC patients with normal underlying liver and can be effective because of antineoplastic and antiangiogenic properties. We also support the use of repeated aggressive surgery with adjuvant chemotherapy and antiangiogenic therapy, which provided complete remission in our patient with metastatic and recurrent FLHCC.

REFERENCES