Refractory malignant hepatocellular tumor consisting of hepatocellular carcinoma and hepatoblastoma in a 10-year-old male

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Abstract

Although hepatoblastoma constitutes most of hapetic tumours in chidren, other types of tumors are often observed in older patients. We report a case of a 10-year-old Japanese boy with a transitional hepatic tumour consisting of both hepatoblastoma and hepatocellular carcinoma. After surgery and chemotherapy with cisplatin and pirarubicin, the tumour regressed, however, new tumours in the liver evolved with element of hepatocellular carcinoma. He died as a result of hepatic failure afte lenvatinib and drug-eluting transcatheter arterial chemoembolisation 18 months after diagnosis. Examinations of a panel of genomic alterations did not identify any therapeutic targets.

Introduction

More than 90% of hepatic malignant tumours in paediatric patient are hepatoblastomas. However, we should suspect of hepatocellular carcinoma (HCC) if a patient is older than 10 years old [1)]. Although most HCCs in adult patients are associated with hepatitis B virus, hepatitis C virus or alcoholic and non-alcoholic fatty liver disease, the causes of HCC in paediatric patients remain unclear[1), 2)]. In adult patients with HCC, hepatectomy, radiofrequency ablation, transcatheter arterial chemoemboliasation (TACE), and liver transplantation are treatment options[2)]. Recently, multikinase inhibitors, including sorafenib and lenvatinib, were approved for treatment of those with HCC[3)]. However, a therapeutic strategy for paediatric patients with HCC has not yet been established. In addition, pathological examination often reveals variations, including fibrolamellar type, epithelial type and clear cell carcinoma[1)]. Transitional hepatic tumours, which have components of both HCC and hepatoblastoma, were also reported in paediatric patients [4), 5)]. We report a case of refractory transitional hepatic tumour.

Case presentation

A 10-year-old Japanese boy presented to our department with intense abdominal pain, frequent vomiting, and hypotension (blood pressure, 76/49 mmHg). The laboratory findings were as follows: white blood cell count, 20.1 $\times$ 10^9/L; red blood cell count, 2.47 $\times$ 10^{12}/L; haematocrit, 20.3%; haemoglobin, 6.8 g/dL and platelet count, 33.8 $\times$ 10^9/L; C-reactive protein, 0.11 mg/dL; aspartate aminotransferase, 86 U/L; alanine aminotransferase, 20 U/L; lactate dehydrogenase, 351 U/L; uretic acid, 8.0 mg/dL; alpha fetoprotein (AFP), 3615 ng/ml and protein induced by vitamin K absence-II, 1493 mAU/ml. Computed tomography (CT) scan revealed a tumour of 8.5 inches in diameter in the right hepatic lobe and massive ascites (Figure1. a, b), suggesting bleeding from a ruptured tumour. The patient undewent emergent coil embolisation of hepatic arteries of segment 5 and segment 6. After 6 days, a complete tumour resection was performed by partial

hepatectomy by paediatric surgeons. Pathological examination revealed an HCC with negative margin, and the HCC cells were not identified in the ascite. Although the patient's AFP level decreased to 56 ng/ml 45 days after the surgery, it increased again to 135 ng/ml with a small nodule at lower surface of the liver and right lung field, as seen on CT scan. Fluorine-18-fluorodeoxyglucose (FDG) positron-emission tomography (PET)-CT showed mild accumulation of FDG in the nodules. Pathological review of the ruptured tumour revealed a malignant hepatocellular tumour consisting of both HCC and hepatoblastoma (Figure 2. a). Two months after the surgery, the patient received the first course of CITA (cisplatin and pirarubicin), consisting of 16 mg/m^2/day of cisplatin div on days 1 to 5 and 30 mg/m^2 /day of pirarubicin on days 2 and 3. After 2 courses of CITA, the patient's AFP level decreased to 28 ng/ml, and CT showed no lesion. After the sixth course of CITA, AFP level decreased to 6 ng/ml. However, after the seventh course of CITA, the patient's AFP level increased to 31 ng/ml with no lesion shown on CT and FDG PET-CT. Two months later, AFP level increased to 302 ng/ml, and CT revealed a nodule at the lower surface of the liver. The lesion was resected by paediatric surgeons, and pathological examination revealed mainly HCC (Figure 2. b). AFP level further increased and multiple lesions in the bilateral lobes of liver developed (Figure1.c,d). Finally, lenvatinib was administered and drug-eluting beads TACE with epirubicine was performed by interventional radiologists. A panel of oncogenes were tested and no actionable targets were identified though ATRX splice site 370 + 1 G >T was noted as an oncogenic mutation. The patient died as a result of hepatic failure. The total duration of clinical course was 18 months.

Discussion

Several clinical studies reporting hepatoblastomas have constructed a therapeutic strategy consiting mainly of chemothrapy and surgery[6)-9)]. A chemotherapy course composed of platinum and anthracycline has been used as a standard treatment [6), 7)]. An appropriate chemotherapeutic regimen for paeditric patients with HCC has not been established because the number of the cases is low and pathological findings are different from that of adults. Indeed, progonosis for the patients remains poor [10)]. In parallel, HCCs in paediatric patients may not be biologically similar to HCCs in adult patients [1)]. In the current case, pathological examination review revealed a malignant hepatic tumour consisting of HCC and hepatoblastoma. That is, the tumour had regions of HCC and lesions of hepatoblastoma. Prokurat et al. [4)]and Ozcan et al. [5)] reported cases of the hepatic tumours, such as transitional liver cell tumours, which were structured by the components of both HCC and hepatoblastoma.

In the current case, CITA chemotherapy decreased the AFP level slowly, and lesions by CT resolved. It suggested that CITA was effective for the components of hepatoblastoma. Then, the patient's serum AFP increased again and it was caused by enlargement of HCC component, which was revealed by the pathological findings of the specimen obtained at the second surgery. Lenvatinib has recently been approved for treatment of HCCs in Japan because it was reported that lenvatinib was non-inferior to sorafenib in overall survival in advanced HCC in adult patients[3)]. Conceivably, administering a multikinase inhibitor, such as lenvatinib, combimed with CITA, might be able to control HCC components although the utility of this combination was not reported previously. We tried lenvatinib after relapse of the disease and a positive effect was not observed.

Genomic variations have also been revealed in hepatic tumours[11), 12)]. In the current case, the results of the oncogene panel did not show any actionable variation. ATRX splice site mutation observed in our patient was reported in also low-grade glioma[13)], but not in HCC. Differential analysis of a panel of oncogenic mutations may clarify the similarity and difference in hepatic tumors of children and adults.

Conflicts of interest

The authors declare no conflicts of interest.

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FIgure LegendS

Figure 1. a,b. Contrast enhaced CT scan revealed hepatic tumour in the right hepatic lobe and ascites at the diagnosis. The patient was not able to lie spine because of abdominal pain. **c.** MRI findings; dynamic T1-weighted showed multiple disseminations as low-intensity area within hepatic lobe 4 months after the last course of CITA. **d.** Then, there was FDG accumulation in the lesions by FDG PET-CT.

Figure 2. a . The specimen resected by the first surgery. Pathological examination (Hematoxylin and Eosin) showed the resions of HCC and hepatoblastoma. The left half of the picture showed the component of HCC, the cells with high nucleus-cytoplasmic ratio. And the right is hepatoblastoma, the cells with a large central eosinophilic nucleolus and a clear cytoplasm. **b.** The specimen resected at the relapse revealed mainly HCC.