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Persistent response to combination therapy of pemigatinib and chemotherapy in a child of combined hepatocellular-cholangiocarcinoma with FGFR2 fusion

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Abstract

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA), an extremely rare and underinvestigated subtype of primary liver cancer in children, generally has a poor prognosis and greater aggressiveness. Histological diagnosis of cHCC-CCA is difficult because of its diverse components, including hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). cHCC-CCA shares some genetic alterations with HCC and CCA. However, only a few studies on genetic alterations in fibroblast growth factor receptor 2 (FGFR2) in cHCC-CCAs have been reported in adults. Therapeutic strategies for cHCC-CCAs are limited, and surgical resection is the only standard of care. No standard systemic treatment has been established for unresectable cHCC-CCAs. Herein, we report a rare case of a 14-year-old female patient diagnosed with unresectable cHCC-CCA with multiple liver masses and metastases to the lungs, lymph nodes and peritoneum. Next-generation sequencing (NGS) has identified an FGFR2-PRDM16 fusion, which has not been previously reported as a common FGFR2 fusion. The blood tumour markers alpha-fetoprotein (AFP) and carbohydrate antigen 19-9 (CA19-9) were both elevated. The patient was treated with pemigatinib (a selective FGFR inhibitor) in combination with Gemcitabine and Cisplatin at our hospital. After three cycles of the combination therapy, the patient achieved a partial response and normalization of tumor markers. After seven cycles of combination therapy, the patient achieved stable disease with the best response. Subsequently, the patient was administered received pemigatinib and gemcitabine. As of the last follow-up date, the patient has survived for 26 months. To the best of our knowledge, this is the first reported rare case of unresectable cHCC-CCA with FGFR2-PRDM16 fusion in a child successfully treated with a combination of pemigatinib and chemotherapy as a first-line regimen. This treatment combination may be effective and safe for patients with unresectable cHCC-CCAs.

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Main text

Pediatric primary liver cancer (PLC) is uncommon, accounting for just 0.5-1.5% of all childhood cancers. It consists of a heterogeneous group of tumors, with the predominant types being hepatoblastomas (HB), accounting for 70% of the cases, followed by conventional hepatocellular carcinomas (HCC), accounting for 27% of the cases. Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare and underinvestigated subtype of PLC in children, with a reported incidence of 0.4-14.2% of PLCs in adults [1, 2]. Patients with cHCC-CCA generally have a poor prognosis and are considered to be poorer than those with HCC and equal to or worse than those with CCA [3, 4].

Owing to the presence of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), the histological diagnosis of cHCC-CCA is difficult and full of challenges [5]. A consensus paper had provided simplified terminology and refined the diagnostic criteria for cHCC-CCA. Surgical resection is the only curative option for patients with resectable cHCC-CCA [2, 5]. However, most patients with cHCC-CCA are often diagnosed at an advanced stage and are not suitable for surgical resection. cHCC-CCA is currently contraindicated for liver transplantation [2, 6]. However, there is no standard systemic treatment or evidence-based management for unresectable cHCC-CCA. Therefore, treatment regimens for HCC or CCA have often been used as systemic therapies for cHCC-CCAs. Although some cHCC-CCA had similar genetic alternations to HCC or CCA, many cHCC-CCA cases reported that does not have so-called "actionable" genetic alterations. Advances in sequencing technology have revealed frequent recurrent alterations in TERT, TP53, KRAS, ARIDIA and IDH1/2 in cHCC-CCA [6, 7]. However, fusions in FGFR2 gene were few reported, with only detected in 0-6.5% of cHCC-CCA [8]. Despite the numerous compounds under development targeting FGFR, the number of clinical trials and availability of these drugs in children with different cancers are quite low. Thus far, cHCC-CCA has shown greater aggressiveness and a dismal prognosis [6, 9].

To our knowledge, this is the first report of a rare case of unresectable cHCC-CCA with an FGFR2-PRDM16 fusion in a child. The patient was successfully treated with a combination of pemigatinib (a selective FGFR inhibitor) and chemotherapy as a first-line regimen.

Case presentation

A 14-year-old Hispanic girl presented to the emergency department with persistent, sharp epigastric pain. She had intermittent, slight upper right epigastric pain for one year, persistent abdominal pain and weight loss of 8 kg over the past two months, and no complaints of fever, abdominal distention, local trauma, or anorexia, and with no significant past medical history of liver cirrhosis or any other relevant underlying liver disease. Family history was negative for malignancies, chronic gastrointestinal illnesses or diabetes mellitus. Ultrasonograpghy (US) revealed multiple heterogeneous masses with irregular lobulated borders. Magnetic resonance imaging (MRI) of the abdomen and computed tomography (CT) of the chest revealed multiple masses with a maximal 6.0×5.0 cm mass in the liver, multiple pulmonary metastases, lymph node metastases, and ascites. The serum AFP (520ng/ml) and CA19-9 (178U/ml) were both elevated. She was scheduled for percutaneous liver tumor biopsy, which confirmed HB in a local hospital. The lesion was positive for epithelial membrane antigen (EMA), weakly positive for cytokeratin (CK)7 and glutamine synthetase (GS), and negative for CD99, CK19, AFP, HCC, β-catenin, GPC3, hepatocytes, and syn. The lesion contained no common genetic mutations known as HB, including TERT, CTNNB1 exon 3 and APC. Symptomatic treatment was initiated with a DSA-guided transcatheter hepatic arterial infusion and chemoembolization with epirubicin (50 mg). The symptoms showed transient remission, and the patient was then referred to our hospital for further treatment.

On admission, physical examination was unremarkable and vital signs were within normal limits. Abdominal examination revealed tenderness in the right upper quadrant with a negative Murphy sigh and no hepatosplenomegaly was observed. Laboratory findings showed alanine aminotransferase (ALT) of 52 IU/L, aspartate aminotransferase (AST) of 72 IU/L, an international normalized ratio (DDI) of 1.01, with a negative for hepatitis B and C panel, and a normal albumin level. Then, the patient underwent an repeat MRI of the abdomen with and without contrast, which showed multiple masses with a maximal 9.2×9.8 cm mass in the liver, with normal common hepatic and common bile ducts. No typical radiological features of HB have been observed. Pathologic analysis showed foci of tumor cells negative for hepatocyte antigen and β-catenin, positive for CK7 and elevation of CA19-9 was more supportive of focal biliary differentiation. Patient age is also an important factor in the differential diagnosis of hepatic tumors.

Subsequently, a multidisciplinary team (MDT) was required. At that time, a repeat liver biopsy was recommended. During the follow-up, the patient had extensive abdominal pain and declining performance status and was treated with cisplatin monotherapy on day 1(80 mg/m^2/day). The CTA revealed an extensive peritoneal and omental metastasis after 20 days of cisplatin treatment. In October 2022, laparoscopic-guided liver biopsy and excision of the omental lesion were performed. Histological sections from the liver tumors were reviewed by three board-certified liver and pediatric pathologists. Microscopically, the tumor was composed of solid, tubular, and trabecular components. Most neoplastic cells exhibited slightly larger and focally prominent nucleoli with frequent mitosis. These features were consistent with those of hepatocellular differentiation. The non-neoplastic liver was non-cirrhotic. And immunohistochemistry revealed atypical cells with bidirectional hepatocellular differentiation, with the expression of HSP70 and glutamine synthetase, and ductal differentiation, with CK7 and CK19 expression, leading to a diagnosis of cHCC-CCA. IHC of the tumor site revealed negative results for PD-1 and PD-L1 expression. Hybrid capture-based NGS (OncoPanScan, Genetron Health) was performed on the biopsy specimen and revealed an FGFR2-PRDM16 fusion (exon 17: exon 4) with a mutation frequency of 7.8% in this patient, which is not a common FGFR2 fusion. Based on the immunohistomorphology and review of the 2018 International Consensus on cHCC-CCA, the final diagnosis was concluded to be an unresectable cHCC-CCA with multiple metastases to the lungs, lymph nodes, and peritoneum (Stage IV, FGFR2-PRDM16 fusion).

The patient started Gemcitabine 800 mg/m^2/day on days 1, 8, and 15, and Cisplatin 25 mg/m^2/day on days 1 to 3 of a 21-day cycle for ten cycles in November 2022 (Fig. 1), according to the guidelines for iCCA [2, 6, 9]. Following confirmation of the presence of FGFR2 fusion, the patient was started on pemigatinib (PEMAZYRE™, a selective, potent, oral, competitive inhibitor of FGFR1, FGFR2, and FGFR3) approved in the CCA setting following the results of the seminal clinical trial FIGHT-202[8, 10, 11]. The pemigatinib was 4.5 mg once daily on days 1-14 of December 2022. Pemigatinib was well tolerated by this patient, with the development of only grade 1 toxicities, including alopecia and fatigue. Routine blood monitoring showed no elevation in serum phosphate and calcium levels. No diarrhoea, dysgeusia, hypophosphataemia, hyponatraemia, arthralgia, and stomatitis, or retinal disorders were observed. Therefore, the pemigatinib dose was increased to 9 mg daily from cycle 2 onwards. Symptomatic benefits were noted within 3 weeks of starting pemigatinib therapy. Due to financial implications, the parents have opted for an abdominal CT scan examined every per 3months. The CT scans at cycle 3 showed

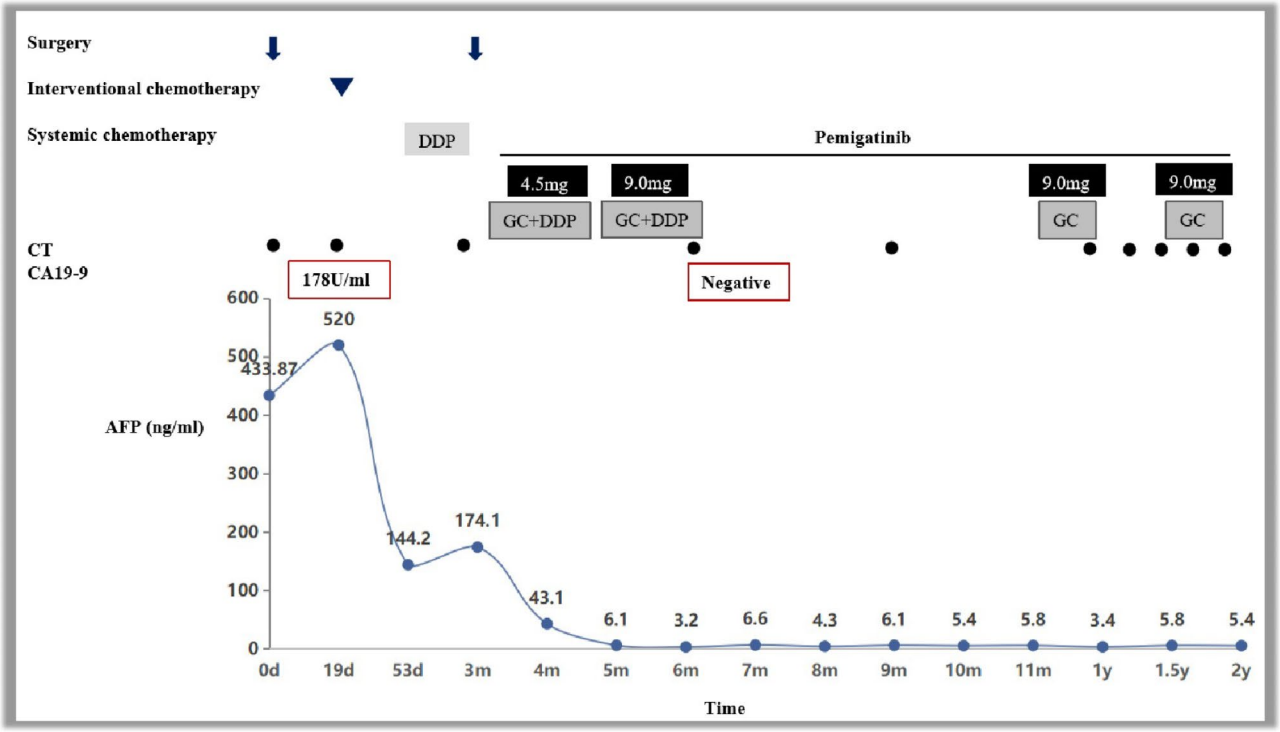

Fig. 1 The timeline of this case. Change of tumor markers (CA19-9 and AFP) through the pre- and postoperative course.Intervenional chemotherapy was DSA-guided transcatheter hepatic arterial infusion and chemoembolization with epirubicin. AFP, alfafetoprotein; CA19-9, carbohydrate antigen 19-9. GC, Gemcitabine; DDP, Cisplatin; CT, computed tomography

partial response (PR; based on the Response Evaluation Criteria in Solid Tumors version 1.1) in the liver (Fig. 2A), and lung metastases (Fig. 2B) at cycle 9 showed stable disease, coupled with significant symptomatic improvement. Serum CA19-9 and AFP levels both decreased to normal levels at cycle 3. Twelve cycles of pemigatinib and gemcitabine continued from September 2023 until the time of reporting. The disease was well controlled, and gradual tumor shrinkage was observed. The patient is still alive two years after starting pemigatinib plus Gemcitabine, Cisplatin treatment.

Discussion

cHCC-CCA is extremely rare in the pediatric population and is poorly understood. It presents with more aggressive behavior and worse survival outcomes. The rarity

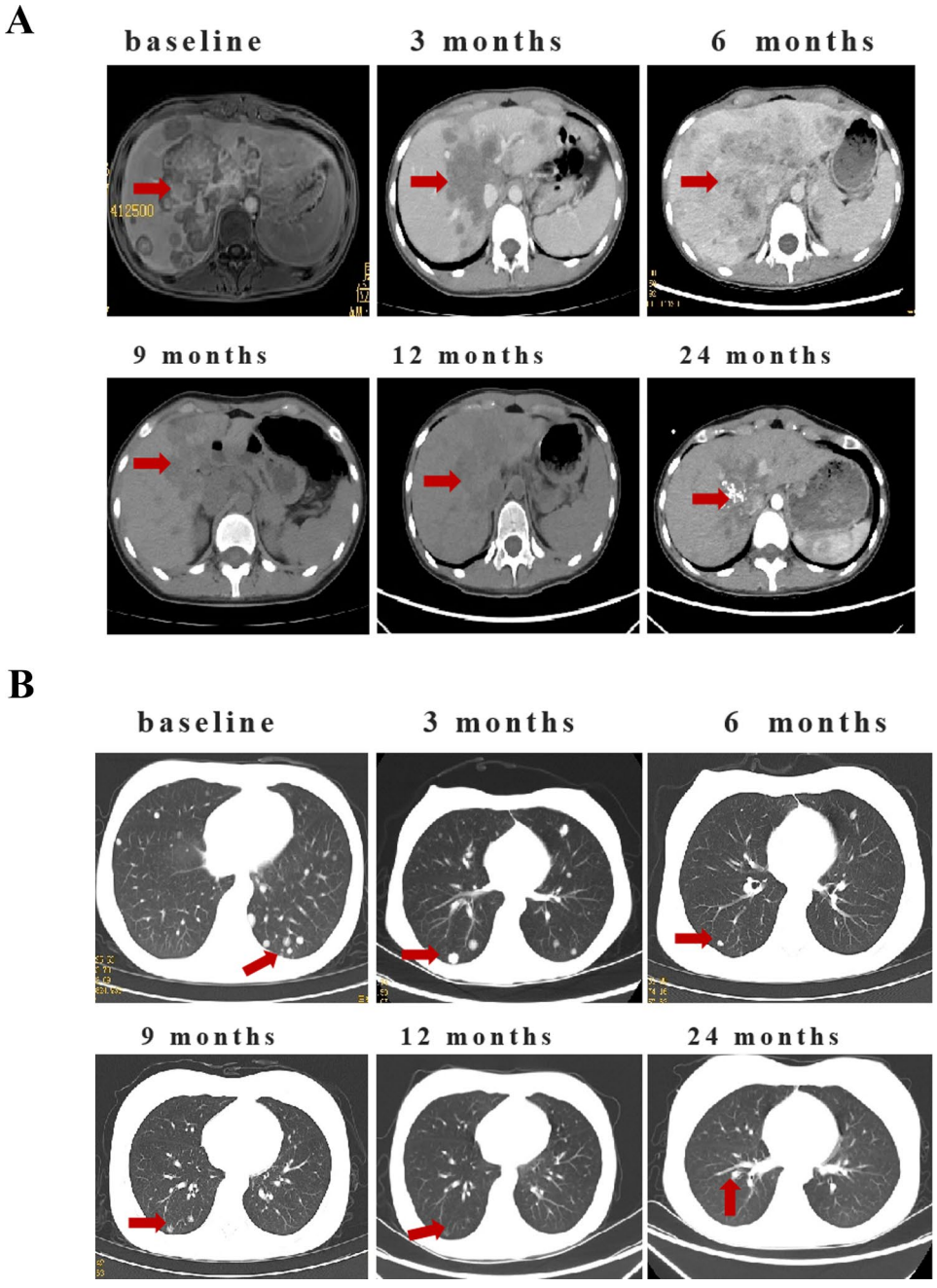

Fig. 2 **A**. MRI of the abdomen showed multiple masses with a maximal 9.2 × 9.8 cm mass (red arrows) in the liver at the start of treatment (baseline). The low signal area in the abdomen CT showed gradual tumor shrinkage at 3 months, 6 months,9 months,12 months, 24 months after of treatment. **B**. Chest CT showed multiple pulmonary metastasis (red arrows) at the start of treament (baseline). The hyperintensity gradually disappeared in lung sites in the early phase

of this tumour remains a challenge in evidence-based management and treatment [2]. It is very problematic to correct pre-surgical diagnosis based on imaging studies and clinical symptoms. The imaging features of cHCC-CCA overlap with those of HCC and CCA depending on the predominant histopathological component. The symptoms in patients with cHCC-CCA are atypical and similar to those observed in patients with HCC or ICC. Therefore, an accurate and timely pathological diagnosis is crucial for optimal cHCC-CCA management.

The ambiguous phenotypic and morphological characteristics of cHCC-CCAs are often problematic for pathologists. The diagnosis of cHCC-CCA is mainly based on the histology of biopsies or surgical specimens. Liver biopsy had an estimated sensitivity and specificity suit for the diagnosis of cHCC-CCA in the presurgical setting. The 2018 International Consensus Group on the Nomenclature of cHCC-CCA recommends that the diagnosis be determined on routine stains, and IHC provides supplemental evidence [1, 10]. In this case, the initial diagnosis was HB based on liver biopsy, which is the most common primary hepatic tumors in the pediatric population within 5 years of age. The vast majority of HB have mutations in the Wnt/β-catenin pathway, which is reflected in a positive nuclear β-catenin by IHC. However, IHC was negative for nuclear β-catenin and AFP, with minimal staining for GS, and the lesion contained no genetic markers known as HB. Furthermore, minimal positive staining for CK7 was more supportive of at least focal biliary differentiation. In cases of diagnostic uncertainty, multiple image-guided biopsies should be performed and analyzed by an experienced clinician. In our study, the degree of mixing of HCC and CCA components was different from that of the first biopsy in the pathological results of the second laparoscopic-guided liver biopsy. Histopathological evaluation of the biopsy or surgical specimens plays a key role in the diagnosis of cHCC-CCA. cHCC-CCA in adults was more common among men and individuals with cirrhosis or chronic liver disease caused by hepatitis B or C viral infections [9–11]. However, most cases of cHCC-CCA have been reported without accompanying chronic liver diseases and arise de novo in the European and American studies[1, 3, 4]. In the present case, the patient had no relevant medical history. The positive rate of AFP (>20 ng/mL) in patients with cHCC-CCA is reported to be lower than that in patients with HCC but higher than that in patients with ICC. Similarly, the levels of CA19-9 in patients with cHCC-CCA were lower than those in ICC but higher than those in HCC [7]. In addition, the simultaneous elevation of AFP and CA19-9 is only observed in a small proportion of cHCC-CCA patients, and its sensitivity for diagnosing cHCC-CCA is only 17.8%[2, 7]. In our study, both AFP and CA19-9 levels were found to be elevated. Although these biomarkers are not specific to cHCC-CCAs and may be found even in non-oncological disorders, an increase in their levels should be investigated.

The management and treatment of cHCC-CCA are based on adults' small retrospective studies. Liver resection is considered the mainstay treatment for cHCC-CCA patients with early stage disease, but a high risk and rate of recurrence have been reported [3–5]. Treatment for patients with unresectable or metastatic cHCC-CCA is restricted to small retrospective studies. Thus, no standard guidelines exist, and systemic drug therapy has been established. Treatment regimens according to the guidelines for either HCC or CCA have often been used as first line chemotherapy for advanced cHCC-CCA in adult patients [2, 3]. In this case, patients were diagnosed at an advanced stage with multiple metastases to the lungs, lymph nodes and peritoneum, and not fit for a surgical resection. The immunoihistochemistry results showed the CCA components were the main part. Combined-type and mixed-type cHCC-CCAs are distinct molecular subtypes. This observation implies that different therapies may be adopted for different cHCC-CCA subtypes, and therapies for iCCA may better suit combined-type cHCC-CCA. Cisplatin and Gemcitabine are a systemic therapy practice standards for iCCA and were initiated as first-line therapy in this case. In addition, the role of liver transplantation remains controversial owing to the historically high recurrence and poor overall survival rates [6]. During treatment, stable disease (SD) with minor lung shrinkage was observed. However, liver transplantation is contraindicated for extrahepatic malignancies that are difficult to cure.

Most cHCC-CCAs lack actionable genetic alterations. A better understanding of the molecular basis of cancer would help to develop targeted therapeutic agents against the druggable genetic aberrations identified in cancer genomes. FGFR2 located on chromosome 10, plays a key role in cell survival and proliferation. FGFR2 genetic alterations have been reported in many solid tumors, most commonly in iCCA (10-16%), endometrial cancer (7.5-11%), and endometrial cancer (3.7-7.9%)[12]. However, FGFR2 was reported in only 0-6.5% of cHCC-CCAs and is considered to be higher in CCA-like cHCC-CCAs [8, 12]. Oncogenic activation of FGFR2 can occur via gene amplification, activating mutations, or chromosomal rearrangement. FGFR2 fusions are the most common FGFR2 alterations found in a various tumor types. Fusions or rearrangements of FGFR2 are found in 10-20% of iCCA, with the most common partner genes being BICC1, PPHLN1, AHCYL1, PARK2, and TACC [12, 13, 14]. FGFR2-PRDM16 fusion has not been reported in cHCC-CCA. The expression pattern of these fusions, in association with sensitivity to FGFR inhibitors, warrants a new molecular classification of cholangiocarcinoma

suggesting a new therapeutic approach to the disease. FGFR2 fusion-positive patients exhibited a younger age of onset, early stage of disease, and longer overall survival, possibly due to FGFR2-targeted treatment in comparison to fusion-negative patients [81214]. Pemigatinib is a competitive inhibitor of FGFR1, FGFR2, and FGFR3, and inhibits receptor autophosphorylation and subsequent activation of FGF/FGFR-mediated signaling networks, leading to the inhibition of tumor cell growth in FGFR-driven cancers [11]. The FIGHT-302 randomized phase III trial is currently ongoing to compare pemigatinib versus cisplatin-gemcitabine as a first-line treatment for CCA patients with FGFR2 fusions/rearrangements. In a large Western multicentric cohort study of cHCC-CCA, tyrosine kinase inhibitors (TKI) or platinum-based chemotherapy had similar efficacy in patients with unresectable or metastatic cHCC-CCA[2, 3, 12, 13]. In a PDX model of iCCA, signaling feedback through the EGFR pathway was found to be the primary agent of adaptive resistance to FGFR kinase inhibition. In monotherapy sensitive and resistant models, EGFR inhibitor combination therapy enhanced FGFRi inhibition, overcame rebound activation of MEK/ERK and mTOR signaling, and induced cell apoptosis[13, 15]. Together, these data support the exploration of FGFR/EGFR dual inhibition as a strategy to improve initial response rates and expand clinical benefits in patients with acquired FGFRi resistance[15]. This may provide useful insights into the choice of appropriate drug treatment for this population, which may increase in the future. In our case, pemigatinib plus chemotherapy was attempted for the first attempt. Our data also showed a promising effect of pemigatinib plus GC chemotherapy as a first-line regimen for pediatric unresectable cHCC-CCA.

In our case, the disease was well controlled after the initiation of pemigatinib plus Gemcitabine, Cisplatin treatment, and gradual tumor shrinkage was observed. Until the end of the follow-up, SD with minor shrinkage was observed after Pemigatinib and Gemcitabine treatment. How to improve the condition is something that we have been thinking about. Retrospective studies have revealed that immune checkpoint inhibitors and platinum-based chemotherapy may provide similar efficacy outcomes in patients with unresectable or metastatic cHCC-CCAs. Programmed death-ligand 1 (PDL1) inhibitor and anti-vascular endothelial growth factor (VEGF) antibody as the current recommended first-line therapy for unresectable or metastatic cHCC-CCA patients showed signs of anti-tumor efficacy[5, 13]. Currently, the standard first-line therapy for CCA involves gemcitabine-cisplatin plus durvalumab. However, IHC showed that PD-1 and PD-L1 were negative in this patient. The tumor mutation burden (TMB) of this patient was 0.94 mutations per megabase. In addition, the microsatellite instability (MSI) status of the sample was microsatellite stable (MSS), suggesting that the patient may benefit less from immune checkpoint inhibitor monotherapy [10]. The therapeutic effect of VEGF antibodies in this regard still needs to be further explored.

Conclusions

A review of the literature showed only one case of cHCC-CCA in a child, which is unlike the case described here. To the best of our knowledge, this is the first reported case of unresectable cHCC-CCA with FGFR2-PRDM16 fusion in a child that was successfully treated with a combination of pemigatinib and chemotherapy. Our data showed the promising effects of this treatment. This treatment combination may be effective and safe for patients with unresectable cHCC-CCAs. In the absence of randomized controlled trials of drug treatments for unresectable cHCC-CCAs, advances in the genetic and molecular characterization of this tumor will contribute to a better understanding of its pathogenesis and will shape its future management.

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Author contributions

Guo-qian He, Qing Li and Jian Li developed the theory and performed the computations. Xia Guo and Ju Gao supervised the findings of this work. All authors discussed the results and contributed to the final version. The authors read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of West China Second Hospital of Sichuan University and followed the Declaration of Helsinki principles (Approval No. 2021-114). Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Consent for publication

Written consent for publication was obtained from all the participants involved in our study.

Competing interests

The authors declare no competing interests.

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