Case Report

Postpartum related intrahepatic cholangiocarcinoma with *FGFR2* fusion and severe hyperbilirubinemia with response to FGFR inhibitor pemigatinib: case report and review

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Background: Cholangiocarcinoma during postpartum or pregnancy is a rare presentation. There are limited cases reported in the literature. Diagnosis can be delayed as presenting signs and symptoms may be attributed to pregnancy or postpartum state.

Case Description: We present the case of a 33-year-old postpartum woman with intrahepatic cholangiocarcinoma with severe hyperbilirubinemia who was found to have fibroblast growth factor receptor 2 (*FGFR2*)-adenosylhomocysteinase like 1 (*AHCYL1*) fusion on next-generation sequencing (NGS). She initially was treated with two doses of gemcitabine and cisplatin with increasing hyperbilirubinemia requiring hold of further chemotherapy. NGS showed *FGFR2-AHCYL1* fusion, and she was started on the FGFR inhibitor pemigatinib, with dramatically decreasing bilirubin within 10 days. She eventually normalized her bilirubin values and had partial response on follow-up imaging.

Conclusions: This is the first report, to our knowledge of response to an FGFR inhibitor in the postpartum setting, as well to show response in the setting of life-threatening hyperbilirubinemia. Our patient did not tolerate standard chemotherapy, likely due to liver dysfunction, but responded to pemigatinib, suggesting that the liver dysfunction was driven by her disease. This case underscores the need to include NGS as part of initial workup to identify important therapeutic targets and increase available lines of therapy, including those patients who are postpartum or pregnant.

Keywords: Cholangiocarcinoma; hyperbilirubinemia; postpartum; fibroblast growth factor receptor fusion (FGFR fusion); FGFR inhibitor; case report

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Introduction

Cholangiocarcinomas are rare malignancies arising from biliary epithelium. Classification is based on tumor cell origin within the biliary tree with subtypes of intrahepatic, perihilar, and distal cholangiocarcinoma (1). A diagnosis in a patient under 40 years of age is unusual except in the setting of primary sclerosing cholangitis (2). Pregnancy or postpartum related cholangiocarcinoma is extremely rare with limited cases reported in the literature.

In this report, we present a case of rapidly evolving cholangiocarcinoma occurring in a healthy 33-year-old postpartum woman with severe hyperbilirubinemia who responded to pemigatinib, a fibroblast growth factor receptor (FGFR) inhibitor. To our knowledge, this is the

first reported case of response in the postpartum setting and in the setting of severe hyperbilirubinemia. We present this case in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-693/rc).

Case presentation

A 33-year-old healthy gravida 2 para 2 (G2P2) delivered a term baby 5 months prior and presented with worsening abdominal pain of 1 month's duration, along with difficulty sleeping, weakness, night sweats, fatigue, and mild shortness of breath. Physical examination demonstrated right upper quadrant abdominal tenderness and jaundice. The total bilirubin was 7.6 mg/dL with direct bilirubin 7.4 mg/dL, alanine aminotransferase (ALT) 798 U/L, aspartate aminotransferase (AST) 580 U/L, and alkaline phosphatase 651 U/L. Kidney function was normal. Alpha-fetoprotein (AFP) was elevated at 404 ng/mL and carbohydrate antigen 19-9 (CA19-9) was normal. *Figure 1* shows a timeline of events in her clinical course, from presentation to the time of death.

Contrast computed tomography (CT) of the abdomen/pelvis with intravenous (IV) contrast showed multiple hypoattenuating hepatic masses, largest in the left lobe, measuring about 9 cm in size, along with confluent widespread lymphadenopathy. Magnetic resonance cholangiopancreatography (MRCP) redemonstrated multiple hepatic masses, largest measuring 11 cm in size along with upper abdominal and retroperitoneal lymphadenopathy as well as an L2 osseous metastasis. Positron-emission tomography (PET)-CT showed fluorodeoxyglucose (FDG)-avid hepatic lesions and lymphadenopathy. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated diffuse malignant appearing biliary strictures not amenable to intervention.

The patient underwent biopsy of right supraclavicular lymph node. Pathology showed moderate to poorly differentiated adenocarcinoma with tumor cells positive for CK7, CDX2 (rare), and albumin in situ hybridization (ISH) (patchy). The tumor cells were negative for CK20, CK5, p40, TTF-1, and PAX8. Liver biopsy demonstrated similar pathologic findings.

Based on imaging and pathology findings, a diagnosis of intrahepatic cholangiocarcinoma was made, and the patient was treated with gemcitabine plus cisplatin while awaiting next-generation sequencing (NGS) results from the supraclavicular lymph node. Unfortunately, her liver function worsened with total bilirubin increasing to 31.8 mg/dL 4 days after initiating chemotherapy. She was hospitalized for urinary tract infection (UTI) with multidrug-resistant *Escherichia coli* and pneumonia. She received a second dose of gemcitabine and cisplatin 2 weeks later (bilirubin 29.2 mg/dL at that time) and was again hospitalized due to multidrug-resistant *Escherichia coli* UTI and *Staphylococcus epidermidis* bacteremia. Due to ongoing infections, further chemotherapy was held. She required paracentesis for symptomatic ascites.

NGS results demonstrated *FGFR2-AHCYL1* rearrangement, but this was seen only on the RNA fusion analysis (addendum). The patient was transitioned to pemigatinib 13.5 mg daily (days 1–14 of a 21-day cycle). Bilirubin was 27.9 mg/dL 2 days prior to starting pemigatinib. Ten days after initiating pemigatinib, the total bilirubin improved to 9.5 mg/dL without any biliary intervention.

After 4 months of therapy, total bilirubin normalized and CT scans showed significant reduction of disease with calcification of liver lesions and decrease in metastatic lymphadenopathy (*Figure 2*). Performance status, jaundice, and ascites markedly improved. *Figure 3* shows a trend of bilirubin levels after both chemotherapy doses and while taking pemigatinib until the patient's death, demonstrating correlation of bilirubin levels with clinical response.

Unfortunately, 6 months post initiation of pemigatinib

Highlight box

Key findings

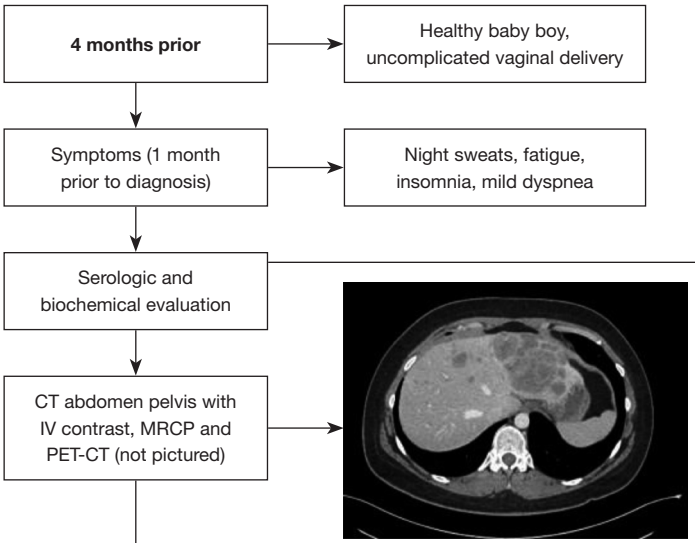
- Cholangiocarcinoma presenting during pregnancy or postpartum state is unusual with very few cases reported in the literature.
- More common presenting disorders of pregnancy or postpartum may confuse or delay diagnosis of cholangiocarcinoma.

What is known and what is new?

- Past treatment of patients with cholangiocarcinoma in postpartum or pregnancy has been limited to chemotherapy.
- We present the first case of postpartum related cholangiocarcinoma to be treated with and respond to the fibroblast growth factor receptor 2 inhibitor, pemigatinib.

What is the implication, and what should change now?

- Next-generation sequencing should be standard part of all workup for patients presenting with advanced cholangiocarcinoma in pregnancy or postpartum state.
- Pemigatinib may be safe at regular doses in liver dysfunction, but additional studies are needed.



Laboratory findings	Result	Reference range
Bilirubin	7.6 mg/dL	<1.2 mg/dL
Direct bilirubin	7.4 mg/dL	0.0–0.3 mg/dL
AST	580 U/L	8–43 U/dL
ALT	798 U/L	7–45 U/dL
Alkaline phosphatase	651 U/L	35–104 U/dL
CA19-9	3 U/mL	<35 U/mL
AFP	404 ng/mL	<8.4 ng/mL

Biopsy	Pathology	Positive by IHC	Negative by IHC
Lymph node biopsy	Moderately differentiated adenocarcinoma	CK7, mucicarmine (focal), CDX2 (rare), albumin ISH (patchy)	CK20, CK5, p40, TTF-1, PAX-8
Liver biopsy	Poorly to moderately differentiated adenocarcinoma	CK7	CK20, CDX2, GATA3, PAX8, ER, WT-1, TTF-1, albumin ISH

Figure 1 Timeline of events from symptoms and diagnosis to death. CT, computed tomography; IV, intravenous; MRCP, magnetic resonance cholangiopancreatography; PET, positron-emission tomography; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CA19-9, carbohydrate antigen 19-9; AFP, alpha-fetoprotein; ISH, in situ hybridization; UTI, urinary tract infection; *FGFR2*, fibroblast growth factor receptor 2; *AHCYL1*, adenosylhomocysteinase like 1; NGS, next-generation sequencing; F/u, follow-up.

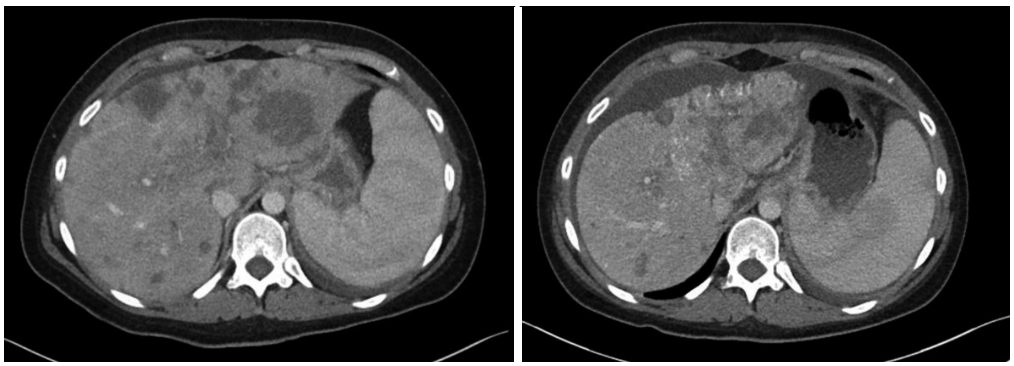


Figure 2 CT abdomen at approximately 2.5 weeks (left) and 4 months (right) after starting pemigatinib. CT, computed tomography.

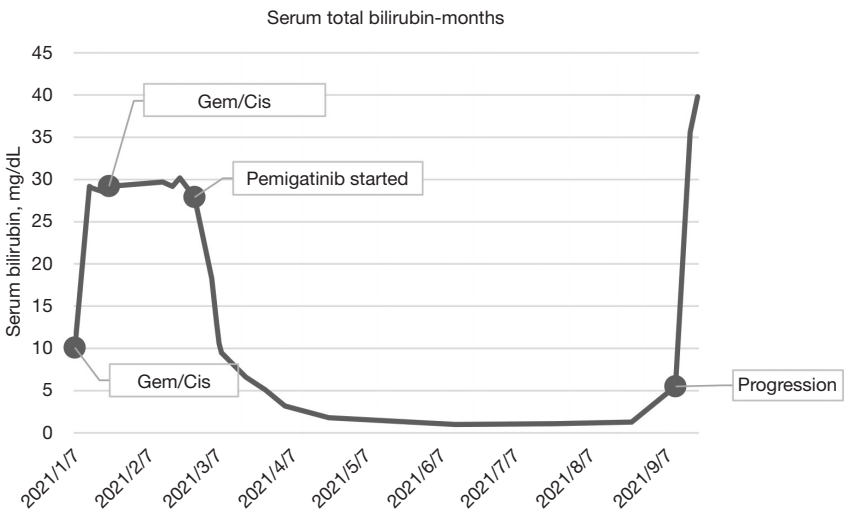


Figure 3 Timeline of events including chemotherapy and pemigatinib with response of total serum bilirubin (mg/dL). Gem/Cis, gemcitabine/cisplatin.

she developed progressive disease with increasing hepatic lesions and ascites along with concern for peritoneal carcinomatosis. The patient underwent Guardant360 testing which revealed multiple new *FGFR2* alterations, including *N549K*, *V564I*, *E565A*, *V564F*, *E565G*, *V564L*, *K641R*, *N549H*, and *N549D*. *BRAF V600E* mutation and *Myc* amplification were also noted. Ultimately her disease progressed too quickly for her to receive additional treatment. She died 9 months after her initial cancer diagnosis. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's family to present her caseand accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

This case report is the first case of cholangiocarcinoma in the postpartum setting to be treated with and respond to the FGFR inhibitor pemigatinib, and the first to show response with no significant safety issues with pemigatinib in the setting of severe hyperbilirubinemia. In fact, there was a dramatic improvement in liver function likely due to tumor response.

Cholangiocarcinoma in pregnancy or postpartum

is a rare condition. To our knowledge, only 12 cases of cholangiocarcinoma occurring during pregnancy or postpartum have been reported between 1998 and 2023. The most common presenting symptoms were nausea, vomiting, abdominal pain, and jaundice. Shared abnormal laboratory values included elevated tumor markers such as CA19-9 or AFP, elevated liver function tests, hyperbilirubinemia and occasionally, coagulation test abnormalities. *Table 1* summarizes the cases of primary cholangiocarcinoma to date based on PubMed database search (English language; search terms cholangiocarcinoma, pregnancy, postpartum) and their treatment course and outcomes (3-14). Seven of these patients received some form of chemotherapy (complete details are not included in those manuscripts).

Due to the small sample size and lack of follow-up details, overall survival and prognosis of these patients are undefined. Several studies have attempted to look at overall prognosis of primary liver cancer cases occurring during pregnancy or postpartum, these have reported conflicting results, largely due to the small sample size and treatment options have changed during this time period (15-17).

Currently, cholangiocarcinoma represents less than 1% of all malignancies and about 10–15% of all primary liver cancer (18). Known risk factors of cholangiocarcinoma include chronic inflammation in the biliary tract from primary sclerosing cholangitis, biliary stones, cirrhosis, and liver infections including liver flukes (Opisthorchis viverrini), hepatitis B virus, and hepatitis C virus (19-21). Our patient did not have any known risk factors for cholangiocarcinoma. Disease was discovered 5 months postpartum and thus, we do not know whether cholangiocarcinoma was present before her pregnancy. Prior literature suggested AFP and placental steroids may contribute to immunosuppressed state of pregnancy (22,23). Estrogen use has also been proposed to promote malignancy in primary liver cancer, however, the data is lacking. Further understanding into the mechanism of disease during pregnancy/postpartum is needed.

For the treatment of advanced cholangiocarcinoma, NGS is highly recommended (24) as targeted therapies are available and life-saving. In the first line, systemic treatments include chemotherapy agents with gemcitabine, cisplatin, and anti-PD-L1 antibody, durvalumab, based on the TOPAZ-1 phase 3 clinical trial (25). This regimen improved overall survival from 11.3 to 12.9 months compared to gemcitabine and cisplatin combination [hazard ratio (HR): 0.76; 95% confidence interval (CI): 0.64–0.91]. This is now the new standard of care first-line regimen and has received Food and Drug Administration approval since September 2022. More recently, KEYNOTE-966 also reported positive results with the combination gemcitabine, cisplatin with an anti-PD-1 antibody, pembrolizumab in improving survival (12.7 *vs.* 10.9 months for gemcitabine and cisplatin; HR: 0.83; 95% CI: 0.72–0.95) (26). Options in the second line include chemotherapy such as FOLFOX [5-fluorouracil (5-FU), leucovorin, and oxaliplatin], 5-FU/liposomal irinotecan, and targeted therapies (27-29). More thorough reviews of systemic treatments including neoadjuvant treatments and targeted agents in cholangiocarcinoma are provided elsewhere (30-33).

FGFR2 alterations are seen in approximately 10–15% of intrahepatic cholangiocarcinoma (34). In April 2020, the oral FGFR inhibitor, pemigatinib, was approved in second line for cholangiocarcinoma with *FGFR2* fusion or other rearrangement based on the single-arm phase II FIGHT-202 trial. In the trial, 146 patients with metastatic or locally advanced cholangiocarcinoma were enrolled to assess the safety and anti-tumor activity of pemigatinib. In the 107 patients with *FGFR2* rearrangement or fusions, 36% achieved objective response including 3 patients with complete response. In the primary analysis, at 17.8 months of follow-up, 82% of 107 patients achieved disease control, with median duration of response 7.5 months. Median progression-free survival was 6.9 months, similar to that seen in the patient presented here (35). Since that time, infigratinib was approved in May 2021 (36) and futibatinib was approved in September 2022 (37), both in second line for unresectable, locally advanced, or metastatic cholangiocarcinoma with *FGFR2* fusion or rearrangement. However, infigratinib is currently no longer available in the US market (38). There are multiple other FGFR inhibitors in development including derazatinib, erdafitinib, zoligratinib, KIN-3248, RLY-4008 (39), and TT-00420 (40).

Acquired resistance and new *FGFR2* mutations develop in patients treated with FGFR inhibitors (41,42). Liquid-based tumor profiling in our patient demonstrated the presence of multiple newly acquired *FGFR2* mutations including *N549K*, *V564I*, *E565A*, *V564F*, *E565G*, *V564L*, *K641R*, *N549H*, and *N549D*. Many of these mutations are thought to arise in the kinase domain, and those affecting the binding affinity of non-selective or ATP-competitive FGFR inhibitors are a likely source of resistance. Research efforts are underway to develop new agents which may be able to overcome mutations in the ATP-binding site or in proximity (43). Goyal *et al.* reported the irreversible FGFR inhibitor TAS-120 (now commercially available as

Table 1 Cases of pregnancy and postpartum related cholangiocarcinoma from 1998–2023

Case	Age (years)	Clinical findings	Gestation	Imaging	Diagnosis	Stage at diagnosis	Outcome/survival
Case 1, Balderston *et al.* (3)	23	Nausea, vomiting, right sided abdominal pain, coagulopathy[†]	26.6 weeks	Ultrasound showed 6 cm cystic hepatic mass; exploration showed massive tumor involving 2/3 liver	Open liver biopsy after correction of coagulopathy was consistent with intrahepatic cholangiocarcinoma	Localized	Not a transplant candidate, patient entered hospice care and died 3 weeks after diagnosis
Case 2, Marasinghe *et al.* (4)	32	Nausea, vomiting fever, icterus, dark urine, right upper quadrant pain, hyperbilirubinemia	16 weeks	Hyperechoic intrahepatic 8–10 cm lesion 4th liver segment	Moderately differentiated cholangiocarcinoma	Locally advanced with positive cystic nodes	Died 2 months after diagnosis from hepatorenal syndrome before she could receive chemotherapy
Case 3, Sadoon *et al.* (5)	39	Pruritus, jaundice, elevated ALT, bile acids, elevated CA19-9, and AFP[‡]	31 weeks with jaundice	Large central liver mass on ultrasound, CT, and MRI	Cholangiocarcinoma per histopathology	Unknown	Extended right hepatectomy followed by chemotherapy, patient alive at publication
Case 4, Stone *et al.* (6)	40	Elevated liver tests, noted at 5 weeks of pregnancy, liver tests rose rapidly post-partum	4 months postpartum	Imaging showed tissue mass in the common hepatic duct; CT, MRI and ERCP with cytology confirmed cholangiocarcinoma	Cholangiocarcinoma per report	Localized, with vascular invasion to trunk of portal vein	Chemotherapy, survival unknown
Case 5, Goswami *et al.* (7)	22	Jaundice, lump in abdomen, dark urine, scleral icterus weight loss, abdominal pain	6 weeks post-partum	CT showed polypoidal lesion filling the common bile duct and cystic duct, dilated gallbladder	Biopsy showed intraductal papilloma with severe dysplasia (IPMN-B, cholangiocarcinoma precursor)	Localized	Outcome and survival unknown
Case 6, Wiesweg *et al.* (8)	38	Back pain, saddle anesthesia, bowel, and bladder dysfunction	18 weeks	MRI showed 5 cm sacral tumor at S1/2, MRI abdomen showed 7.4 cm × 6 cm in hepatic segments 2–4	Cholangiocellular adenocarcinoma	Stage IV, with osseous involvement at S1/2, hepatic satellite nodules and nodes	Spinal decompression with sacral laminectomy; chemotherapy while pregnant with gemcitabine and cisplatin, healthy delivered at 35 weeks; due new osseous metastases, mother resumed gemcitabine/ cisplatin chemotherapy; then received FOLFOX, later weekly epirubicin, died 14 months after diagnosis
Case 7, Malli *et al.* (9)	30	Abdominal pain, elevated CA19-9 to 27,000, known diagnosis of primary sclerosing cholangitis	10 weeks	Ultrasound showed 4.8×2.0×2.7 lesion right lobe	No details given	Stage IV (multifocal disease in liver, pulmonary nodules, and mesenteric/retroperitoneal lymphadenopathy)	Started on chemotherapy with close follow up, survival unknown
Case 8, Qasrawi *et al.* (10)	38	Nausea, epigastric/right upper quadrant pain, dark urine and hepatomegaly[§]	36 weeks	Right hepatic 2.8 cm mass, fatty liver, MRI showed 11.2×9.2 left hepatic lobe lesion with satellite lesions in right hepatic lobe	Adenocarcinoma with phenotypic profile consistent with cholangiocarcinoma	Stage IV (pulmonary nodules likely consistent with metastasis)	Received palliative gemcitabine; complicated by recurrent cholangitis with multi-drug resistant organisms, died 6 months from diagnosis
Case 9, Das *et al.* (11)	28	Right upper quadrant pain and jaundice; postprandial vomiting during pregnancy, fever 10 days postpartum[¶]	10 days post-partum	CT showed hepatomegaly with multiple liver lesions with associated lymphadenopathy	Liver biopsy reported cholangiocarcinoma	Stage IV (lung nodules, nodal disease and L1 lytic lesion)	Received capecitabine with follow up at another hospital, survival unknown
Case 10, Pencovich *et al.* (12)	30	Elevated routine AFP to 1,800 ng/mL, elevated CA19-9 to 914 ng/mL, no symptoms	28 weeks	Ultrasound and MRI showed a 9–10 cm lesion within left lobe	CK7 and CK18 positive adenocarcinoma felt to be consistent with intrahepetic cholangiocarcinoma	Localized to liver	Left extended hepatectomy at 30 weeks, gave birth to healthy baby at 38 weeks, survival unknown
Case 11, Carson *et al.* (13)	26	Incidental finding during lung transplant workup for cystic fibrosis; anorexia, weight loss, subjective fevers	5 months post-partum	CT showed 6.3 cm mass in right liver lobe, MRI suggested intrahepatic cholangiocarcinoma	CK7 positive adenocarcinoma	Stage IV with PET showing uptake in lungs, mediastinal nodes, right iliac and femur bone	Hospice, survival unknown
Case 12, Chow *et al.* (14)	35	Epigastric pain, elevated ALT eventually cholangitis	19 weeks	CT showed hilar mass and MRI showed hilar stricture	Mixed hilar neuroendocrine carcinoma cholangiocarcinoma	Type 4 Klatskin tumor, intrahepatic metastatic spread	Resection followed by multiple courses of chemotherapy/ immunotherapy; died 1 year after diagnosis from hepatorenal syndrome with hepatic encephalopathy

[†], possible HELLP syndrome or DIC; [‡], working diagnosis felt to be obstetric cholestasis; [§], presumed diagnosis was fatty liver of pregnancy; [¶], previous diagnosis was acute fatty liver of pregnancy. ALT, alanine aminotransferase; CA19-9, carbohydrate antigen 19-9; AFP, alpha-fetoprotein; CT, computed tomography; MRI, magnetic resonance imaging; ERCP, endoscopic retrograde cholangiopancreatography; IPMN-B, intraductal papillary mucinous neoplasm of the bile duct; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; PET, positron-emission tomography; HELLP, hemolysis, elevated liver enzymes and low platelet count.

futibatinib) retained activity against nine clinically identified *FGFR2* mutations except *V565F*, outperforming ATP-competitive FGFR inhibitors infigratinib or zoligratinib (44). Furthermore, Sootome *et al.* also reported that futibatinib, when compared to the commercially available ATP-competitive FGFR inhibitors erdafitinib and pemigatinib, was a stronger inhibitor of the *N550K* (hinge) and *V565L* (gatekeeper) mutations (45). KIN-3248 is a new pan-FGFR inhibitor designed to target multiple gatekeeper, activation loop and molecular brake mutations which confer clinical resistance (46). A phase I clinical trial is underway (NCT05242822). Obtaining serial circulating DNA analysis at the time of progression may help identify and tailor future therapies.

To our knowledge, this is the first reported pregnancy-related or postpartum cholangiocarcinoma patient to be treated with an FGFR inhibitor with response both radiographically and clinically. Her multidrug-resistant UTI and bacteremic episodes resolved as disease burden decreased. She was not able to receive subsequent therapy. This is consistent with a previous study that demonstrated that only half of the patients can receive any treatment after progressing on an FGFR inhibitor (41).

Our patient responded to pemigatinib in the setting of severe hyperbilirubinemia. Pemigatinib was never tested in this population, as these patients were excluded from trial. Bilirubin decreased rapidly after starting pemigatinib, suggesting that the underlying malignancy was responsible for the liver dysfunction. This case report suggests that pemigatinib may be safe in severe hyperbilirubinemia due to underlying cancer, but more testing is needed. In addition, blood based NGS testing identified several of the clinically observed mutations which may develop in patients treated with FGFR inhibitors. This finding suggests molecular profiling should be used to follow these patients after exposure to one FGFR inhibitor to help identify resistance mutations and guide next line of therapy. Her aggressive disease course fits with the biology of pregnancy or postpartum cholangiocarcinoma, though the reported cases in the literature of this population are small. Finally, the fact that the *FGFR2-AHCYL1* was seen only on the RNA transcriptome analysis initially underscores the need to perform RNA sequencing with DNA sequencing at diagnosis to avoid missing potentially actionable mutations (47).

Conclusions

In summary, pregnancy/postpartum associated cholangiocarcinoma has an aggressive clinical course. Discovery of the *FGFR2* fusion in intrahepatic cholangiocarcinoma has led to development of FGFR inhibitors which can produce objective responses in these patients. In this patient with postpartum associated intrahepatic cholangiocarcinoma, we demonstrate objective and durable response to the FGFR inhibitor, pemigatinib, with progression-free survival similar to that reported previously. Our patient tolerated the treatment well despite hyperbilirubinemia suggesting that pemigatinib can potentially be safely administered at regular dose in patients with liver dysfunction. Molecular profiling with a tailored therapy approach should be the standard workup for all newly diagnosed cholangiocarcinoma, including those patients who present in pregnancy or the postpartum period.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-693/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-693/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-693/coif). N.T. is a recipient of the 1K23MD017217-01A1. She has received honorarium from Helsinn and is a consultant for tempus, AZ and genentech. The other authors have no conflicts of interest.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's family for the publication of this case report and

accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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