

Cholangiocarcinoma in pregnancy: a case report

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A 35-year-old pregnant woman presented at 19 weeks of gestation with epigastric pain and mildly elevated alanine transaminase level. She subsequently developed acute cholangitis, with deteriorated liver function. Imaging revealed features of cholangiocarcinoma. Termination of pregnancy was performed at 22 weeks of gestation to facilitate maternal treatment. She underwent hepatectomy, followed by multiple courses of chemotherapy and immunotherapy. However, she died from hepatorenal failure with hepatic encephalopathy 1 year later. Cholangiocarcinoma in pregnancy is rare. Although it is a differential diagnosis of deranged liver function in pregnancy, a precise diagnosis can be challenging as the presenting signs and symptoms are not obvious.

Case presentation

In June 2019, a 35-year-old, gravida 2, para 1 woman with a history of cesarean section for breech presentation 8 years earlier presented at 19 weeks of gestation with epigastric pain, and mildly elevated alanine transaminase (ALT) level. The antenatal blood test results were all normal, including negative hepatitis B surface antigen. The first trimester Down syndrome screening showed low risk for Down syndrome. Blood tests showed mildly deranged liver function, with elevated ALT level up to 78 IU/L while the alkaline phosphatase level (90 IU/L) and the total bilirubin level (10 $\mu\text{mol/L}$) were normal. She did not have any drug or herbal medication exposure. Her pain gradually subsided and her ALT level decreased to 52 IU/L 2 days later. She was discharged with liver function monitoring in outpatient clinic.

One week later, her ALT level elevated to 124 IU/L and her alkaline phosphatase level elevated to 335 IU/L, but the total bilirubin level was normal at 14 $\mu\text{mol/L}$. At 21 weeks of gestation, she was asymptomatic with no fever or epigastric pain. Morphology scanning showed normal fetal morphology. Blood test results for hepatitis C antibodies and hepatitis B surface antigen were negative.

She was admitted to our hospital for further examination. While awaiting ultrasonography of the liver and assessment by the medical team, she developed right upper quadrant pain, with on and off fever up to 38.8°C. At 2 days after admission, blood tests showed elevated bilirubin level up to 53 $\mu\text{mol/L}$, ALT level up to 162 IU/L, aspartate transaminase level up to 92 IU/L, and gamma-glutamyl transferase level up to 186 IU/L. The clinical picture was compatible with acute cholangitis complicating

pregnancy. Intravenous antibiotics was started. Ultrasonography of the liver revealed a dilated intrahepatic duct with a 3-cm ductal stone and sludge at confluence as well as a prominent common duct. Magnetic resonance cholangiopancreatogram showed evidence of a high-grade hilar stricture causing severe bilobed intrahepatic ductal dilatation, with features of cholangiocarcinoma (CCA). A 2.5-cm ductal stone with small fluid level was noted within the grossly dilated segment 8 and 4 intrahepatic duct (Figure). These were compatible with the clinical findings of superimposed acute cholangitis. Contrast computed tomography showed a tumour at the hilar region suggestive of CCA (Figure). A multidisciplinary team involving hepatobiliary surgeons, oncologists, radiologists, obstetricians, and midwives was arranged for the patient and her family. The need for percutaneous drainage to treat the biliary obstruction and the plan for definitive surgical treatment for CCA were explained. The option of termination of pregnancy to facilitate investigation and treatment was discussed, as was an alternative option of conservative management after percutaneous drainage and then delivery of the fetus in late second trimester and then surgical treatment for the CCA. The possible delay to the maternal treatment, the potential for high estrogen levels in pregnancy to aggravate the CCA, and the risk of prematurity complications of the baby resulting from early delivery were also discussed. The family opted for termination of pregnancy at 22 weeks of gestation.

Percutaneous transhepatic biliary drainages were performed. Pus aspirated from the right intrahepatic

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Figure. Transverse view of (a) T1-weighted and (b) T2-weighted magnetic resonance cholangiopancreatogram showing an abrupt change in calibre with tight stricture at the hilar region (arrows) causing severe bilobed intrahepatic ductal dilatation and a 2.5-cm stone (arrowheads) within a grossly dilated S8/4 intrahepatic duct. (c) Coronal view of contrast computed tomography showing an enhancing soft tissue tumour with irregular margin (arrowhead) leading to stricture at the hilar region (arrow).

duct yielded *Clonorchis sinensis* ovum and *Klebsiella pneumoniae*. Biliary sepsis was resolved. Positron emission tomography-computed tomography confirmed

the metastatic CCA. A hepatobiliary surgeon was consulted, and surgery remained the only effective method to improve survival. The patient underwent resection of the liver lesion (right trisectionectomy, caudate lobectomy, and hepaticojejunostomy). A type-4 Klaskin tumour with multiple intrahepatic metastases in the right liver was confirmed intra-operatively. Histopathology showed a metastatic hilar mixed neuroendocrine carcinoma-CCA, with direct invasion to the liver and extensive lymphovascular invasion and perineural invasion. She underwent multiple courses of chemotherapy and immunotherapy, but the disease continued to progress. One year after the diagnosis, she died from hepatorenal failure with hepatic encephalopathy.

Discussion

CCA is a slow-growing heterogeneous group of malignancy arising from the biliary epithelium. It can be classified based on its anatomical location (extrahepatic, intrahepatic, and perihilar). It most commonly affects patients aged 50 to 70 years¹. Most cases are asymptomatic at early stages, and presentation is usually delayed, with locally advanced or metastatic disease at the time of diagnosis². CCA is the second most common hepatic malignancy, accounting for 3% of all gastrointestinal cancers and 10% to 15% of primary liver cancers¹⁻³. Its incidence has been increasing in recent decades worldwide, with a much higher incidence in North Thailand and South Korea compared with the West³. In Hong Kong, the age-standardised incidence of CCA is 2.3 cases per 100 000 population^{2,3}. The aetiology of CCA in Asian countries is mostly related to infection, especially with liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis*. *Clonorchis sinensis* infects fish-eating mammals and is actively transmitted in Korea, China, and Vietnam⁴. A meta-analysis reported that the relative risks of CCA with infection of liver fluke was 4.8 (95% confidence interval, 2.8-8.4)⁵.

Liver diseases complicate the courses of about 3% of all pregnancies and may have detrimental effects on the mother and fetus, but CCA during pregnancy is rare. In PubMed database, 14 such cases have been identified during 1975 to 2019⁶⁻¹⁹. Patients were aged 25 to 40 years, and no risk factor was identified in most patients. Common clinical manifestations include nausea, vomiting, abdominal pain, pruritus, jaundice, and hepatomegaly. For cases with laboratory results, liver enzymes (aspartate transaminase / ALT) and total bilirubin levels were either within normal range or elevated up to 2 to 3 times the upper limit for liver enzymes and up to 5 times the upper limit for bilirubin. Gamma-glutamyltransferase level was measured

in three cases only and all were markedly elevated. The symptoms of CCA mimic some pregnancy-specific conditions with abnormal liver function such as obstetric cholestasis, HELLP syndrome (haemolysis, elevated liver enzymes, and a low platelet count), and acute fatty liver of pregnancy (AFLP)^{9,13,15}. In addition, differential diagnoses of deranged liver function not related to pregnancy include drug- or toxin-induced hepatitis and viral hepatitis⁹. Patients diagnosed with CCA usually portend poor prognosis given the delayed diagnosis and aggressive nature of disease^{1,2}. Of the 14 cases, 8 died shortly (2 weeks to 6 months) after diagnosis. Pregnancy may adversely affect the prognosis of hepatocellular carcinoma, as gestational suppression of the immune system may aggravate tumour progression and aggression^{9,14}. Pregnancy increases oestrogen levels and may aggravate a pre-existing malignant liver disease^{12,14}. However, data for these rare conditions are lacking, and the effect of pregnancy on the progression and prognosis of CCA remains unclear.

Deranged liver function in pregnancy is related to pregnancy-specific conditions and primarily occurs in the third trimester, with incidence varying from 59.2% to 84%²⁰⁻²². Common differential diagnoses include pre-eclampsia with hepatic impairment, HELLP syndrome, obstetric cholestasis, and AFLP²⁰⁻²³. The pattern of abnormal liver function differs in these differential diagnoses. In pre-eclampsia, liver function tests show a 2-to-5-fold increase in ALT level, with normal serum bile acids and total bilirubin level, whereas in HELLP syndrome, ALT level is more significantly elevated, with one case reporting a 30-fold increase²⁰. HELLP syndrome is also associated with low haemoglobin level, low platelet counts, and raised lactate dehydrogenase level. In obstetric cholestasis, patients usually present with severe pruritus without rash in the third trimester, with moderately elevated (1.5- to 8-fold) transaminase level and increased total serum bile acid level²³. In AFLP, the elevated transaminase level is wide (3- to 15-fold), with increased total bilirubin level²⁰. Compared with HELLP syndrome, AFLP is associated with more severe hypoglycaemia (70%), hyperuricaemia (90%), coagulopathy (90%), and leukocytosis²³. On the contrary, in

CCA, liver function tests often show obstructive patterns, with normal aminotransferase levels, except in acute obstruction or cholangitis in which aminotransferase levels are markedly increased²¹.

Surgical resection remains the only potentially curative option for CCA²⁴. In most cases, babies are delivered prematurely to facilitate investigations and treatment when the diagnosis is suspected or confirmed. In only one case, the patient underwent extended left hepatectomy for intrahepatic CCA at 30 weeks of gestation while continuing the pregnancy and eventually had a normal vaginal delivery at 38 weeks of gestation⁸. In the management of malignancy, early treatment and long-term outcome should be prioritised⁸. An optimal management strategy is to balance between the risk of continuing pregnancy and the potential harm to fetus against the benefits of treatment to the mother. Decision should be made based on the gestational age and the extent of spread or staging of the disease and the recommended course of treatment in non-pregnant women^{25,26}. Our patient was at 22 weeks of gestation at the time of diagnosis of CCA. The fetus was not viable and may have inevitable complications of prematurity had the patient decided to keep the pregnancy. Balancing the risk of disease progression and the risk of prematurity of the fetus, termination of pregnancy was the optimal decision.

Conclusion

CCA is a slow-growing disease and usually presents late with metastasis, with poor prognosis. CCA in pregnancy is rare and its diagnosis challenging. Treatment plan should take into account both maternal and fetal well-being and strike a balance between both.

Acknowledgement

The authors would like to thank Dr Yu San Ming, Consultant of Radiology Department, United Christian Hospital for his assistance in preparing the figures.

Declaration

The authors have no conflicts of interest to disclose.

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