Two cases of hepatoblastoma with neonatal necrotizing enterocolitis

Sidou He¹, Xisi Wang¹, Chao Duan¹, Wen Zhao¹, CHIYI JIANG¹, Shihan Zhang², Binglin Jian¹, Wei Yang³, Tong Yu⁴, Libing Fu⁵, Huanmin Wang⁶, and Xiaoli Ma¹

¹Beijing Children's Hospital Capital Medical University
²Beijing Children's Hospital, Capital Medical University
³Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
⁴Beijing Children's Hospital, Capital Medical University, No. 56 Nanlishi Road, Beijing 100045, China.
⁵Beijing Children's Hospital, Capital Medical University, Beijing, China.
⁶National Center for Children's Health(Beijing), Beijing Children's Hospital, Capital Medical University, Beijing, China

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Abstract

Hepatoblastoma (HB) is the most common liver malignant tumor in childhood and is related to premature delivery and low birth weight. Neonatal necrotizing enterocolitis (NEC) is also related to premature delivery and low birth weight. We report two patients who were diagnosed as hepatoblastoma after having a history of NEC, and they are not common in hepatoblastoma due to their particularity. Premature delivery and low birth weight are the common factors leading to the onset of HB and NEC. The correlation between the two needs further study.

INTRODUCTION

Hepatoblastoma is the most common primary malignant hepatic tumor of infancy and childhood, occurring predominantly in the first two years of life¹. While the etiology of HB remains unknown, it has been found to be associated with low birth weight, Beckwith–Weidemann syndrome, preterm delivery, polyhydramnios, and eclampsia/severe preeclampsia²,³. Several factors are associated with the prognosis of HB, including completeness of tumor removal, serum alpha-fetoprotein (AFP) levels, tumor size, tumor multifocality and distant metastases, etc⁴. NEC is among the most common and lethal gastrointestinal diseases that plague premature infants, leading to high short-term and long-term morbidity and mortality⁵. We report two cases of premature infants who had a history of NEC and were diagnosed with hepatoblastoma. Patient and disease characteristics are summarized in Table 1.

1.1 Patient 1

A 5-month-old male child, IVF, was delivered at 28 weeks and weighted 1260g at birth. Mother gestational age is 32 years old and in good health during pregnancy. One month after the patient was born, it was found that there was no obvious inducing abdominal distension, accompanied by anorexia. The imaging examination revealed neonatal necrotizing enterocolitis, surgery was performed. An ileal fistula was found 3 months later and liver enlargement was found during surgery. Serum Alpha-fetoprotein (AFP) was 560,537ng/mL. Abdominal enhanced CT confirmed obvious strengthening in most of the enhanced lesions and weak enhancement in low-density areas on plain scan. The lesion was about 9.2×7.3×9.6cm in the left lobe of the liver, involving the 1/2 hepatic hilum. Chest CT, Cranial MRI showed no obvious abnormalities. Histologic
examination confirmed (liver) malignant tumors, most likely hepatoblastoma. Immunohistochemical staining showed GS(+),CK(+),Hepatocyte(+),Ki-67 30%(+),HSP70(+),GPC-3(+),CgA(-),SYN(-),Vimentin(-). Hepatoblastoma diagnosed on June 22, 2018, PRETEXT II. According to the CCCG-HB-2016 protocol6, AFP decreased significantly to 11619ng/mL after 3 cycles of C5V chemotherapy. Afterwards, Driver DNA Assay results showed that ARID1A stop mutation and CTNNB1 missense mutation. However, AFP increased to 133218ng/mL after 4 courses of chemotherapy, so the chemotherapy regimen was changed to C5VD. AFP decreased to 117706ng/mL after 2 courses of treatment. Surgical treatment was performed on October 23, 2018. Histologic examination confirmed an epithelial (fetal) hepatoblastoma. AFP decreased to 13702ng/mL after the first course of C5VD chemotherapy. AFP decreased to the lowest point of 74.87ng/mL at the end of 4 courses, and then increased again to 174.83ng/mL at the end of 5 courses. Therefore, the chemotherapy regimen was changed to ICE (cyclophosphamide,etoposide,carboplatin) treatment for 2 courses in the high-risk group, but AFP continued to rise to 496.543ng/mL. CT scans of the chest and abdomen showed no obvious abnormalities. Due to the long duration of chemotherapy, the doctor recommended regular monitoring of AFP and stopping the chemotherapy on March 7, 2019. Subsequently, AFP increased gradually, but abdominal enhanced CT showed no specific lesions. After 3 months of discontinuation, AFP increased to 6101ng/mL. Abdominal enhanced CT confirmed nodular high-density shadows on the left edge of the liver, and chest CT showed nodular shadows on both lungs. Therefore, tumor recurrence and distant metastasis are considered. After 3 cycles of platinum-based chemotherapy, the lung tumor was removed on September 3, 2019. Postoperative pathology supported hepatoblastoma lung metastasis. 6 courses of platinum-based chemotherapy were given postoperatively After that, AFP and chest and abdomen images were reexamined regularly. In June 2020, AFP was progressively increased again, and abdominal ultrasonography showed tumor recurrence in situ in the left lobe of the liver. Partial hepatectomy was performed on August 24, 2020. AFP is 417.8ng/mL after 4 cycles of platinum-based chemotherapy. Follow-up until November 30, 2020, the child was 98cm in height, 13.2kg in weight, and in good condition.

1.2 Patient 2

A 3-year-old male child, IVF, was delivered at 27+3 weeks, birth weight 1150g. Intestinal resection and anastomoses were performed for NEC one month after birth. Abdominal mass with no obvious cause was found 2 weeks ago. AFP was 114434ng/mL; Abdominal ultrasonography showed a mass in the right lobe of the liver (6.2x4.5x4.1cm), which was considered to be a hepatoblastoma. Abdominal enhanced CT revealed masses of low density and heterogeneous enhancement mass of 6.87x4.94x3.8cm in the right dorsal lobe of the liver (Fig. 1). Chest CT and Cranial MRI showed no obvious abnormalities. Due to the high location of the tumor and its close relationship with the inferior vena cava and the right diaphragmatic surface, Ultrasound-guided percutaneous biopsy could not be performed, so the patient was clinically diagnosed as hepatoblastoma on July 7, 2018, PRETEXT II. According to the CCCG-HB-2016 protocol6, the AFP was reduced to 4088 ng/ml after 4 cycles of C5V chemotherapy, and surgery was planned. However, after 2 weeks of chemotherapy interval, AFP increased to 21,235ng/mL preoperatively, so the chemotherapy regimen was changed to C5VD, and AFP dropped to 7,324ng/mL after 1course of chemotherapy. The operation was performed on November 7, 2018. Histologic examination confirmed epithelial (embryonal mixed and fetal) hepatoblastoma. AFP decreased to normal 2.38ng/mL after 2 courses of chemotherapy. After 5 courses of treatment, chemotherapy was stopped on February 10, 2019.After that, AFP and chest and abdomen imaging were normal. Follow-up until November 30, 2020, AFP was in the normal range, there was no obvious abnormality in chest and abdominal imaging. At present, the child is 120cm in height and 18kg in weight. He is in good health.

2 DISCUSSION

HB usually occurs in the context of inherited conditions, such as Beckwith -Weidemann syndrome, familial adenomatous polyposis coli, and trisomy 18 syndrome1. The high incidence of HB is also associated with low birth weight and small gestational age7,8. The results of the Peggy Reynolds study indicate that children with very low birth weight (<1500 g) have a significantly increased risk of hepatoblastoma in the study7. Children with a gestational age of <33 weeks and younger children also have a higher risk of HB9. The two
children we reported were both premature babies with a birth weight of <1500g. Patient 1 was born at 28 weeks and had a birth weight of 1260g; patient 2 was born at 27+3 weeks and had a birth weight of 1150g, which is consistent with the above conclusions.

The mother’s age is too high or too low, the mother’s smoking, the mother’s weight, and the use of infertility treatments increase the risk of HB. Pu Conghun and others also observed infants whose mothers are >20 years old and >30 years old have an increased risk of developing hepatoblastoma compared to infants whose mothers are 20 to 29 years of age. In this article, the mothers of the two cases of children were more than 30 years old. The maternal age of patient 1 was 32 years old, and the maternal age of patient 2 was 38 years old, which is consistent with the above conclusion.

In addition, it is worth noting that two cases of children had a history of NEC. Preterm birth and low birth weight are currently the most consistent risk factors for NEC development. Very premature infants (EPT <28 weeks) are considered the highest risk. The incidence is negatively correlated with gestational age and birth weight. The smaller the gestational age, the lower the birth weight, and the higher the incidence.

A Cochrane study showed that compared with formula feeding, breast-fed preterm infants have a 2.77-fold lower risk of developing NEC. In this article, both children received artificial feeding after birth, which was a factor worth considering.

Patient 1 Driver DNA Assay showed that ARID1A stop mutation and CTNNB1 missense mutation. ARID1A is a tumor suppressor gene that is mutated in a variety of human cancers, and is mutated in 10-15% of liver cancers. In 2017, Sun et al. found that ARID1A has environment-dependent tumor suppressor and carcinogenic effects in cancer. In HB, CTNNB1, which encodes β-catenin, is the most frequently mutated driver proto-oncogene, with a mutation frequency of 50-90%. Point mutations and in-frame deletions in CTNNB1 exon 3 have been reported as the main causes of HB. ARID1A stop mutation and CTNNB1 missense mutation are also a factor of poor prognosis in children.

Study showed that AFP decreased by less than 60% and tumor size decreased by less than 50% after neoadjuvant chemotherapy were significant independent prognostic risk factors for the 3-year RFS rate. The first manifestation of recurrent patients was the elevation of AFP, but there is no significant recurrence in ultrasound and CT examination. It provides an accurate prognostic prediction for HB. In this report, AFP gradually increased after the patient stopped chemotherapy, but no obvious abnormality was observed in imaging at the beginning, which later indicated tumor metastasis and recurrence. However, the AFP of the patient remained normal after 2 courses of chemotherapy. In patients with complete tumor resection, AFP gradually increases to the abnormal range, indicating tumor recurrence or distant metastasis. This is also an indicator of a poor prognosis in Patient.

Hepatoblastoma is rarely diagnosed in children with a history of NEC. This is a very interesting and reportable case. After analysis, we believe that NEC and HB share common risk factors. Premature delivery and low birth weight are common factors contributing to the disease. As for the correlation between the two, no relevant literature has been reported so far, and further study is needed.

CONFLICT OF INTEREST
The authors declare that there is conflict of interest.

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REFERENCES


11. Pu C. Retrospective analysis of maternal and infant birth features of hepatoblastoma patients.


**Figure legend** Transversal CT sections of the liver tumor in patient 1.

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TABLE 1 Patient and disease characteristics.docx available at https://authorea.com/users/470695/articles/562666-two-cases-of-hepatoblastoma-with-neonatal-necrotizing-enterocolitis