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CASE REPORT

CANCER INNOVATION

Hepatoblastoma with neonatal necrotizing enterocolitis: Two case reports

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Abstract

We report two children with hepatoblastoma (HB) with a history of neonatal necrotizing enterocolitis (NEC). Case 1 was diagnosed with HB at 5 months of age. Liver enlargement was found during the NEC operation at 3 months of age and then was clinically diagnosed by imaging. After six chemotherapy courses, a partial hepatectomy was performed. Three months after ceasing the chemotherapy, a chest computed tomography scan suggested that distant metastasis of the tumor should be considered, and the lesion was removed. However, 9 months after the operation, alpha-fetoprotein concentrations were increased, and abdominal imaging showed a recurrence of the tumor in situ, resulting in a hepatectomy. Case 2 was diagnosed with NEC shortly after birth and underwent an intestinal resection and anastomosis 1 month later. He was diagnosed with HB at 3 years of age. Hepatectomy was performed after five courses of chemotherapy. Chemotherapy was stopped after 10 courses, and alpha-fetoprotein concentrations were normal. At present, both children have survived and are in a healthy condition. Physicians should be aware of the possibility of HB and a history of NEC in children. Premature birth and low birth weight are common factors leading to the pathogenesis of HB and NEC. The association between these two diseases requires further study.

Abbreviations: AFP, Alpha-fetoprotein; CT, Computed tomography; HB, Hepatoblastoma; NEC, Neonatal necrotizing enterocolitis.

Sidou He and Xisi Wang are co-first authors of the article.

KEYWORDS
hepatoblastoma, LGR5, low birth weight, neonatal necrotizing enterocolitis, premature delivery

1 | BACKGROUND

Hepatoblastoma (HB) is the most common primary malignant hepatic tumor in infancy and childhood, occurring predominantly in the first 2 years of life [1]. While the etiology of HB remains unknown, it is associated with low birth weight, Beckwith-Weidemann syndrome, preterm delivery, polyhydramnios, and eclampsia/severe preeclampsia [2]. Several factors, such as the completeness of tumor removal, serum alpha-fetoprotein (AFP) concentrations, tumor size, tumor multifocality, and distant metastases, are associated with the prognosis of HB [3]. Neonatal necrotizing enterocolitis (NEC) is among the most common and lethal gastrointestinal diseases that occur in premature infants, leading to high short-term and long-term morbidity and mortality [4]. We report two cases of premature infants who had a history of NEC and were diagnosed with HB. This report mainly discusses the etiology and pathogenesis between NEC and HB. The patients' and disease characteristics are shown in Table 1.

2 | CASE PRESENTATION

2.1 | Case 1

A 5-month-old boy, who was conceived by in vitro fertilization, was delivered at 28 weeks and weighed 1260 g at birth. One month after delivery, abdominal distension occurred with no known cause. An imaging examination showed NEC and surgery was performed. An ileal fistula was found 3 months later, and liver enlargement was noted during surgery. The serum AFP concentration was 560,537 ng/mL, and an abdominal enhanced computed tomography (CT) scan showed a lesion of approximately 9.2 cm × 7.3 cm × 9.6 cm in the left lobe of the liver. Chest CT and cranial magnetic resonance imaging showed no apparent abnormalities. A histological examination confirmed a malignant tumor, which was most likely HB. Therefore, the tumor was clinically diagnosed as HB, PRETEXT II. According to the CCCG-HB-2016 protocol [5], the AFP concentration was greatly decreased (11,619 ng/mL) after three cycles of C5V chemotherapy. A Driver DNA assay then showed an

TABLE 1 Two cases' disease characteristics.

	Case 1	Case 2
Sex	Male	Male
Gestational age (weeks)	28	27 + 3
Birth weight (g)	1260	1150
Maternal pregnancy age (years)	32	38
Age at diagnosis of HB	5 months 12 days	3 years and 2 months
PRETEXT	II	II
AFP (ng/mL)	560,537	114,434
TBIL (μmol/L)	62.25	5.94
Pathological type	Fetal type	Mixed fetal and embryo
Tumor size	9.2 cm × 7.3 cm × 9.6 cm	6.87 cm × 4.94 cm × 3.8 cm
Disease sites	Left lobe of liver, lung metastasis	Right dorsal lobe of liver
Medical history	NEC	NEC
treatment	Chemotherapy, primary tumor resection	Chemotherapy, primary tumor resection
Follow-up time (months)	54	53
Outcome	Disease progression	Disease remission

Abbreviations: AFP, serum alpha-fetoprotein; HB, hepatoblastoma; NEC, neonatal necrotizing enterocolitis; TBIL, total bilirubin.

ARID1A stop mutation and *CTNNB1* missense mutation. However, after four courses of treatment, the AFP concentration increased to 133,218 ng/mL. The chemotherapy regimen was adjusted to C5VD and continued for two courses, and the AFP concentration decreased to 117,706 ng/mL. Tumor resection was performed and postoperative histopathology suggested HB. After receiving four courses of C5VD chemotherapy after surgery, the AFP concentration decreased to a nadir of 74.87 ng/mL. After five courses of surgery, AFP concentrations increased, which led to a change in the chemotherapy regimen to ifosfamide, carboplatin, and etoposide with two courses of chemotherapy (cyclophosphamide, etoposide, and carboplatin). However, the AFP concentration then increased to 496.543 ng/mL. CT scans of the chest and abdomen showed no apparent abnormalities. Thirteen courses of chemotherapy were performed over a long time. Therefore, the chemotherapy was stopped and AFP concentrations were monitored regularly. Three months following the discontinuation of chemotherapy, AFP concentrations increased to 6101 ng/mL, and abdominal enhanced CT showed nodular high-density shadows on the left edge of the liver. Chest CT showed nodular shadows on both lungs, which suggested tumor recurrence and distant metastases. The lung tumor was removed following three cycles of platinum-based chemotherapy. Postoperative pathology indicated HB lung metastasis. An additional six platinum-based chemotherapy courses were administered postoperatively, and AFP concentrations and chest and abdominal images were regularly re-examined. Nine months after the lung surgery, AFP concentrations progressively increased again, and abdominal ultrasonography showed a recurrence of the tumor in situ in the left lobe of the liver. Partial hepatectomy was performed. The AFP concentration was 417.8 ng/mL following four cycles of platinum-based chemotherapy. After 54 months of follow-up, our patient is still in stable partial remission in accordance with the criteria for evaluating the primary tumor response of solid tumors.

2.2 | Case 2

A 3-year-old boy, who was conceived by in vitro fertilization, was delivered at 27 + 3 weeks and his birth weight was 1150 g. Intestinal resection and anastomoses were performed for NEC 1 month after birth, and an abdominal mass with no known cause was found 2 weeks later. The AFP concentration was 114,434 ng/mL. Abdominal-enhanced CT revealed masses of low density and a heterogeneously enhanced mass of 6.87 cm × 4.94 cm × 3.8 cm in the right dorsal lobe of the liver (Figure 1). Chest CT and cranial magnetic resonance imaging showed no apparent abnormalities. An ultrasound-guided percutaneous biopsy of the tumor could not be performed owing to the high location of the tumor and its close relationship with the inferior vena cava and right diaphragmatic surface. Therefore, the clinical diagnosis was HB, PRETEXT II. According to the CCCG-HB-2016 protocol [5], four cycles of C5V chemotherapy were performed. An abdominal CT scan showed that the size of the lesion in the right lobe of the liver (3.2 cm × 2.4 cm × 2.7 cm) was smaller than previously observed. The AFP concentration was reduced to 4088 ng/mL. Surgery was then scheduled. After a 2-week chemotherapy interval, the AFP concentration increased to 21,235 ng/mL preoperatively, which led to a change in the chemotherapy regimen to C5VD. After an additional course of chemotherapy, the AFP concentration decreased to 7324 ng/mL, and tumor resection was performed. A histological examination confirmed HB. After three courses of chemotherapy for postoperative C5VD, the AFP concentration returned to normal (2.38 ng/mL). Ten courses of chemotherapy were administered to the child. AFP concentrations and chest and abdominal imaging were normal. After 53 months of follow-up, our patient is still in stable complete remission in accordance with the criteria for evaluating the primary tumor response of solid tumors.

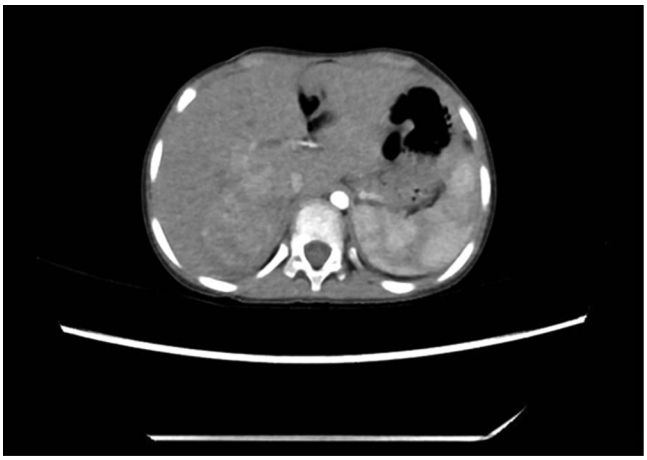

FIGURE 1 Transversal computed tomography sections of a liver tumor in case 2.

3 | DISCUSSION AND CONCLUSIONS

HB is the most common primary pediatric liver tumor. It is usually diagnosed during the first 3 years of life, and most cases are sporadic [6]. Pu et al. reported that infants whose mothers are younger than 20 years or older than 30 years have an increased risk of developing HB [7]. In the current report, the mothers

of both children were older than 30 years. The high incidence of HB is generally associated with low birth weight and early gestational age [8]. Children with a very low birth weight (<1500 g) have an increased risk of HB [8]. Children with a gestational age of <33 weeks and younger children also have a higher risk of HB [9]. Notably, both of the children in the current report had a history of NEC. Preterm birth and low birth weight are also the most consistent risk factors for the development of NEC [10]. The two children in this report were premature infants with a birth weight of <1500 g.

In case 1, an ARID1A stop mutation and CTNNB1 missense mutation were detected. ARID1A is a tumor suppressor gene that is mutated in various human cancers and in 10%–15% of liver cancer [11]. In HB, CTNNB1, which encodes β-catenin, is the most frequently mutated driver proto-oncogene, with a mutation frequency of 50%–90% [12]. Point mutations and in-frame deletions in exon 3 in CTNNB1 have been reported as the leading cause of HB [13]. ARID1A stop mutations and CTNNB1 missense mutations are also factors of a poor prognosis in children.

Liver damage occurs in NEC. Inflammatory cytokines produced in the gut enter the liver through portal blood flow. In addition, the liver produces inflammatory cytokines, such as tumor necrosis factor-α and interleukin-18 [14]. These cytokines can cause liver damage. A study using myeloperoxidase immunostaining showed neutrophil infiltration in the liver in the NEC group [15]. Leucine-rich repeat-containing Gprotein-coupled receptor 5 (LGR5) is a marker of stem cells in the gut, stomach, hair follicles, and breast. In contrast to the colon and intestines, LGR5 stem cells are not present in the steady-state liver, but occur during tissue damage [16].

HB is rarely diagnosed in children with a history of NEC. Therefore, the findings of our patients are important. Premature delivery and low birth weight are common factors contributing to HB and NEC. Therefore, further study is required to determine whether there is an association between HB and NEC.

AUTHOR CONTRIBUTIONS

Sidou He: Writing—original draft (equal). **Xisi Wang**: Writing—review and editing (equal). **Chao Duan**: Supervision (equal). **Wen Zhao**: Formal analysis (equal). **Chiyi Jiang**: Methodology (equal). **Shihan Zhang**: Data curation (equal); investigation (equal). **Binglin Jian**: Methodology (equal). **Wei Yang**: Data curation (equal). **Tong Yu**: Formal analysis (equal). **Libing Fu**: Methodology (equal). **Huanmin Wang**: Investigation (equal). **Xiaoli Ma**: Project administration (equal); supervision (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

ETHICS STATEMENT

This case report was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University (IEC-C-006-A04-V.06).

INFORMED CONSENT

Written informed consent was obtained from our patient's parents for publication of this case report, all information contained within it, and any accompanying images. Copies of the written consent are available for review by the Editor of this journal.

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REFERENCES

1. Sharma D, Subbarao G, Saxena R. Hepatoblastoma. Semin Diagn Pathol. 2017;34(2):192–200. https://doi.org/10.1053/j.semdp.2016.12.015
2. Ansell P, Mitchell CD, Roman E, Simpson J, Birch JM, Eden TOB. Relationships between perinatal and maternal characteristics and hepatoblastoma: a report from the UKCCS. Eur J Cancer. 2005;41(5):741–8. https://doi.org/10.1016/j.ejca.2004.10.024
3. Qiao GL, Li L, Cheng W, Ge J, Zhang Z, Wei Y. Predictors of survival after resection of children with hepatoblastoma: a single Asian center experience. Eur J Surg Oncol. 2014;40(11):1533–9. https://doi.org/10.1016/j.ejso.2014.07.033
4. Baranowski JR, Claud EC. Necrotizing enterocolitis and the preterm infant microbiome. Adv Exp Med Biol. 2019;1125:25–36. https://doi.org/10.1007/5584_2018_313
5. Association PCPC. Expert consensus multidisciplinary management of hepatoblastoma (CCCG-HB-2016)[J]. Chin J Pediatr Surg. 2017;10(38):733–9. https://doi.org/10.3760/cma.j.issn.0253-3006.2017.10.003
6. Czauderna P, Lopez-Terrada D, Hiyama E, Häberle B, Malogolowkin MH, Meyers RL. Hepatoblastoma state of the art: pathology, genetics, risk stratification, and chemotherapy.

Curr Opin Pediatr. 2014;26(1):19–28. https://doi.org/10.1097/MOP.0000000000000046
7. Pu CL, Guo CB, Jin XQ, Deng C, Zhang MM, Li YC, et al. [Retrospective analysis of maternal and infant birth features of hepatoblastoma patients]. Zhonghua Gan Zang Bing Za Zhi. 2009;17(6):459–61.
8. Oue T, Kubota A, Okuyama H, Kawahara H, Nara K, Kawa K, et al. Hepatoblastoma in children of extremely low birth weight: a report from a single perinatal center. J Pediatr Surg. 2003;38(1):134–7. https://doi.org/10.1053/jpsu.2003.50027
9. Heck JE, Meyers TJ, Lombardi C, Park AS, Cockburn M, Reynolds P, et al. Case-control study of birth characteristics and the risk of hepatoblastoma. Cancer Epidemiol. 2013;37(4):390–5. https://doi.org/10.1016/j.canep.2013.03.004
10. Berkhout DJC, Klaassen P, Niemarkt HJ, de Boode WP, Cossey V, van Goudoever JB, et al. Risk factors for necrotizing enterocolitis: a prospective multicenter case-control study. Neonatology. 2018;114(3):277–84. https://doi.org/10.1159/000489677
11. Mathur R. ARID1A loss in cancer: towards a mechanistic understanding. Pharmacol Ther. 2018;190:15–23. https://doi.org/10.1016/j.pharmthera.2018.05.001
12. Crippa S, Ancey PB, Vazquez J, Angelino P, Rougemont AL, Guettier C, et al. Mutant CTNNB1 and histological heterogeneity define metabolic subtypes of hepatoblastoma. EMBO Mol Med. 2017;9(11):1589–604. https://doi.org/10.15252/emmm.201707814
13. Liu L, Wang J, Sun G, Wu Q, Ma J, Zhang X, et al. m^{6}A mRNA methylation regulates CTNNB1 to promote the proliferation of hepatoblastoma. Mol Cancer. 2019;18(1):188. https://doi.org/10.1186/s12943-019-1119-7
14. Halpern MD, Holubec H, Clark JA, Saunders TA, Williams CS, Dvorak K, et al. Epidermal growth factor reduces hepatic sequelae in experimental necrotizing enterocolitis. Neonatology. 2006;89(4):227–35. https://doi.org/10.1159/000090015
15. Miyake H, Li B, Lee C, Koike Y, Chen Y, Seo S, et al. Liver damage, proliferation, and progenitor cell markers in experimental necrotizing enterocolitis. J Pediatr Surg. 2018;53(5):909–13. https://doi.org/10.1016/j.jpedsurg.2018.02.006
16. Huch M, Dorrell C, Boj SF, van Es JH, Li VSW, van de Wetering M, et al. In vitro expansion of single Lgr5+ liver stem cells induced by Wnt-driven regeneration. Nature. 2013;494(7436):247–50. https://doi.org/10.1038/nature11826

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