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Case Report

# A Case of Congenital Hepatoblastoma Coexisting with Pulmonary Hypertension

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**Abstract**

Hepatoblastoma (HBL) is the most frequently detected malignant tumor of the liver in childhood. HBLs detected antenatally or up to 3 months after birth are considered congenital HBLs. We report a five-day-old female infant in whom a hepatic mass was detected at 20 weeks' gestation. At birth (36 weeks), the hepatic mass measured 12x6 cm, and she had respiratory distress. Pulmonary hypertension (PHT) was detected on echocardiographic evaluation. Despite dual medical therapy, her PHT did not improve. Histologically, the biopsy demonstrated a mixed epithelial-mesenchymal HBL with predominance of fetal morphology in the epithelial component. Chemotherapy was initiated on postnatal day 15; however, the baby died of respiratory failure on postnatal day 23. Conclusion: HBL is an embryonal tumor which can develop early in the intrauterine period. Although the mechanism is not known, it may cause PHT which would affect the prognosis negatively.

**Keywords:** Congenital, Hepatoblastoma, Pulmonary hypertension

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## Introduction

Hepatoblastoma (HBL) is a rare tumor of childhood and its frequency in the first year of life is about one in a million.[1] Cases that are detected antenatally or in the first three months of the postnatal period are considered as congenital HBL.[2] Fewer than 10% of HBL cases are diagnosed in the neonatal period.[3] Genetic and environmental factors such as familial adenomatous polyposis syndrome, Beckwith-Wiedemann syndrome, eclampsia or severe preeclampsia, low birth weight, prematurity, and smoking are associated with an increased risk of HBL.[2] In the literature, the gestational age of cases that were detected in the antenatal period varied between 23–42 weeks.[4] The most frequently detected histologic type is epithelial type, with mixed epithelial-mesenchymal type detected less frequently.[2,5] To the best of our knowledge, no cases of coexisting congenital HBL and pulmonary hypertension (PHT) have been reported in the literature. In this report, we present a mixed epithelial/mesenchymal HBL at 20 weeks' gestation, complicated after birth by PHT.

## Case Report

We report a 5-day-old female infant who was delivered at 36 weeks' gestation via cesarean section for decreased fetal movement. Antenatal ultrasonography exams performed from the beginning of the 20th week of gestation showed a hepatic mass that filled the entire abdomen. The neonate was intubated and administered surfactant due to respiratory distress. At the time of admission, physical examination was as follows: body temperature 36.5°C, heart rate: 158/min, respiratory rate: 62/min, blood pressure: 73/33 mm Hg, and peripheral oxygen saturation 86%. Physical examination revealed severe abdominal distention and a solid palpable mass was detected 10 cm below the right costa. The mass extended towards the left of the midline and was palpable 5 cm below the left costal margin. Complete blood count was as follows: hemoglobin: 10.4 g/dL, hematocrit: 31%, mean corpuscular volume (MCV): 112.7 fL, mean corpuscular hemoglobin (MCH): 32.6 pg, white blood cells (WBC): 17900/mm$^3$ and platelet count: 103000/mm$^3$. Biochemistry investigation showed the following: aspartate aminotransferase (AST): 253 U/L (0–110U/L), alanine aminotransferase (ALT): 54 U/L (0–5U/L 2), gamma glutamyl transferase (GGT): 159 U/L (5–36U/L), lactate dehydrogenase (LDH): 952 U/L(225–500U/L), total bilirubin 7.8 mg/dL, direct bilirubin 3.5 mg/dL, alpha fetoprotein (AFP): 66.862 IU/mL (2892–61157 IU/mL). Dynamic magnetic resonance imaging (MRI) of the abdomen showed a giant mass originating from the liver, which was 12x6 cm in size.

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The mass had a rich vascular structure and hypointense nodules, the largest of which was 5 mm (Figure 1). Echocardiography revealed a secundum atrial septal defect (4 mm), patent ductus arteriosus (2.2 mm), and PHT. The right ventricular systolic pressures measured by peak tricuspid regurgitation velocity were 50 mm Hg (postnatal day 1), 40 mm Hg (postnatal day 9), 40 mm Hg (postnatal day 14), and 45 mm Hg (postnatal day 20). The right ventricular systolic pressure, which we obtained using peak tricuspid regurgitation velocity, was higher at 30 mmHg, consistent with PHT. First, sildenafil (postnatal day 1) was initiated, and then an iloprost infusion (postnatal day 9) was administered due to PHT.

Tru-cut biopsy was not performed because the tumor was rich in vascular structure. A laparoscopic wedge biopsy was obtained from the nodular lesions in the liver. Histopathologic examination revealed a mixed epithelial/mesenchymal-type HBL. Microscopic examination revealed extensive necrosis and hemorrhagic areas. The tumor tissue was composed of hepatocyte-like cells with normochromatic nucleus and large eosinophilic cytoplasm (Figure 2). The cells tended to form plates and thick cords that resembled fetal liver. In the large areas, the hyalinized myxoid stroma was remarkable (Figure 3).

The tumor was classified as stage IV because the tumor was detected in all parts of the liver in accordance with the staging of the Pretreatment Extension of Disease Evaluation System (PRETEXT) of the International Childhood Liver Tumors Strategy Group (SIOPEL). A 1.7 mg/kg cisplatin infusion was administered on postnatal day 15 in accordance with the high risk HBL treatment protocol of the Société Internationale d'Oncologie Pédiatrique – Epithelial Liver Tumor (SIOPEL-3). The patient could not tolerate enteral feeding due to the abdominal distension; therefore, parenteral nutrition was initiated. The AFP level decreased to 29 954 IU/mL on day 5 of treatment. Blood oxygen saturation remained low and red blood cell transfusion was administered. Despite increased ventilator support, carbon dioxide retention and hypoxemia worsened progressively. On the 23rd postnatal day, the overall condition of the patient deteriorated gradually; pH was 6.63 and $PCO_2$ was 188 on the patient's blood gas test. Despite supportive treatments and aggressive cardiopulmonary resuscitation, the baby died of respiratory failure on postnatal day 23.

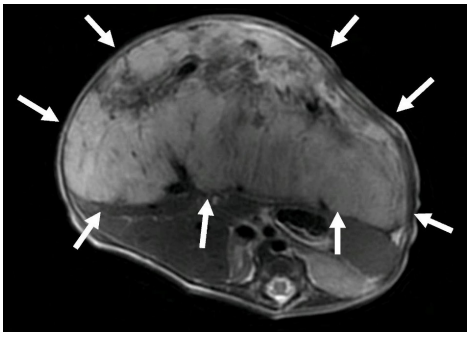

**Figure 1**. The abdominal magnetic resonance imaging shows a diffuse hepatic mass (arrows) which fills the entire abdomen.

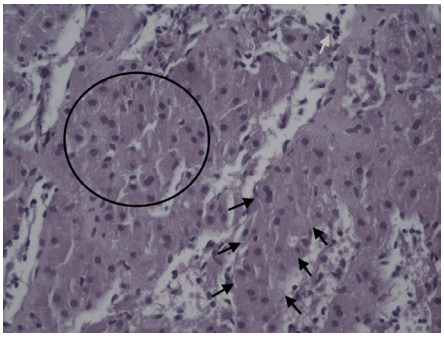

**Figure 2**. Fetal Hepatocyte-Like Cells Tend to Form Plates (Circle) and Thick Cords (Arrows) (H and E, x400).

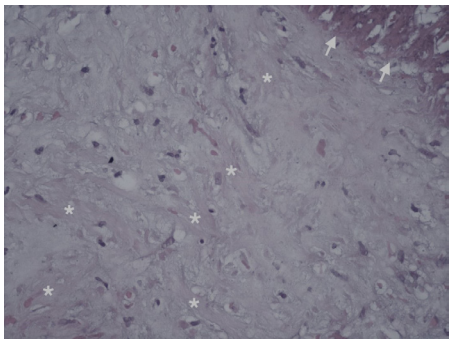

**Figure 3**. Large Myxoid Stroma With Hemorrhagic Areas (Arrows) and Hyalinization (Asterisks) (H and E, x400).

## Discussion

Although hepatoblastomas develop most often in the first two years of life, they can also develop in the perinatal period. One review investigating studies between 1970 and 2012 reported that the gestational ages of 52 patients with congenital HBL were between 30–37 weeks, and masses were demonstrated in the prenatal period in 14 (26.9%) patients. In addition, it was reported that AFP levels were studied in 28 patients; the AFP levels of 8 patients were found in the normal range for the neonatal period. A mesenchymal component was detected in 6 (15.7%) out of 38 patients whose diagnoses were histologically confirmed, and 23 (52%) out of 44 patients whose clinical course had been recorded expired.[2]

It was reported that between 1970 and 2005, 32 (16.5%) patients were diagnosed as having HBL out of 194 who were diagnosed with hepatic tumors, and only 9 patients were demonstrated to have a mass in the antenatal period; the mean gestational week of the patients was 37 (range, 23–42) weeks. In the same study, it was reported that the most frequent finding was high levels of AFP, followed by abdominal distension, anemia, fetal hydrops,

and respiratory distress.[4]

Our patient is the youngest patient reported in the literature to be diagnosed with congenital HBL, with symptoms of severe abdominal distension, respiratory distress, and persistent PHT. Transthoracic echocardiography is a non-invasive method used primarily in the evaluation of PHT. The measurement of the velocity of a tricuspid regurgitation jet is the most commonly used method. Continuous wave Doppler of the tricuspid regurgitation (TR) trace is used to measure the difference in pressures between the right ventricle and right atrium. The simplified Bernoulli equation ($P = 4[TRmax]^2$) is used to calculate this pressure difference using peak TR velocity. A peak TR velocity value of >30 mm Hg is considered as PHT.[6] In neonates, persistent PHT may be idiopathic, but it is usually associated with acute respiratory diseases such as meconium aspiration syndrome, respiratory distress syndrome, pneumonia and congenital diaphragmatic hernia.[7] In these diseases, multiple mechanisms are usually responsible for the development of PHT (alveolar hypoxia, acute pulmonary vasoconstriction, vascular remodeling). Congenital diaphragmatic hernia is accompanied by insufficiency in the pulmonary vasculature and pulmonary hypoplasia.[7]

Abdominal and thoracic cavities are connected to each other via the diaphragm, and intra-abdominal pressure is transmitted to the thoracic cavity through the diaphragm when pressure increases for any reason. The lesions in the abdomen (acid, blood, liquid, and tumor) directly increase intra-abdominal pressure. Elevation of the diaphragm causes compression atelectasis, increase in pulmonary afterload and in alveolar pressure by increasing pleural and intrathoracic pressure and compressing the lungs. On the other hand, vascular compression caused by the mass causes alveolar edema by reducing the blood flow in the vena cava inferior. As a result of these events, intrapulmonary shunts and oxygen consumption increase and lung compliance decreases. The result is carbon dioxide retention and hypoxemia.[8] In our case, the patient had severe distension of the abdomen caused by a massive mass and the patient was never able to tolerate enteral nutrition. In our case, a few of the mechanisms described above may have contributed to the formation of PHT.

Similar to other embryonal tumors, HBL has been suggested to develop due to the persistence of progenitor cells that escape from terminal epithelial differentiation during organogenesis. These cells, which are similar to stem cells, may harbor genetic damage and later cause neoplastic transformation. In addition, studies have shown that activation of components of the Wnt signal pathway, which have a complicated but critical role in the development of the embryonic liver, and mutations of β-catenin might have a role in the pathogenesis of the disease.[9]

HBL is an embryonal tumor that may even develop in the very early intrauterine period. The time of disease development in the intrauterine period, and whether it causes dysfunction in neighboring organs and tissues might be factors that affect the prognosis; however, the significance of these factors have not been clarified. Detection of the responsible genes, and demonstration of the stage when these genes cause the deterioration of organogenesis will provide significant improvement in understanding the pathogenesis of the disease. Thus, the effect of the responsible genes on the prognosis will be clarified, and will translate to data that could be used in clinical practice.

### Authors' Contribution

ZCÖ: conceived and designed the research and righted the manuscript. AÇS and YDK: wrote the manuscript. PK: performed the echocardiography. DA: performed the pathologic examination. ANT and ÖB: completed and revised the manuscript.

### Conflict of Interest Disclosures

The authors report no conflict of interest.

### Ethical Statement

Informed consent was obtained from the patient's parents who agreed to the publication of this case.

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