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Case report

EPITHELIAL HEPATOBLASTOMA IN A MALE INFANT WITH BECKWITH-WIEDEMANN SYNDROME: A CHALLENGING CASE REPORT

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Abstract

Hepatoblastoma (HB) is among the most common pediatric primary liver tumor and constitutes almost 90% of tumors in children, aged 5 years, or younger. Hepatoblastomas are classified based on histological subtypes, which describe the types of cells and tissues present in the tumor. The primary classification divides them into epithelial and mixed epithelial and mesenchymal types. A two-month-old male infant was admitted at the Department of Pediatric Surgery-Clinical Hospital Acibadem Sistina, via referral from a pediatrician, with chief medical complaints of macroglossia, left-sided longitudinal hemi-hypertrophy and facial dysmorphic stigmatic features, for further clinical evaluation. After the initial physical examination, clinical investigations were obtained by protocol. Laboratory results showed elevated levels of lymphocytes, thrombocytes, RDW-SV, and hyperglycemia as well. The levels of alpha-fetoprotein (AFP) were >1000.0 (0-28 kiU/L). Imaging CT scan showed two tumefactions located between the 5th and 6/7th liver segments, clearly demarcated with dimensions of 57 mm (larger lesion) and 33 mm (smaller lesion), while the other intra-abdominal organs appeared normal. An urgent indication for surgical treatment was established, and a right-sided laparotomy was made. Intraoperative findings were two large liver masses located in the right lobe. Cholecystectomy and right partial hepatectomy were performed. Histopathological analysis revealed epithelial hepatoblastoma, embryonal subtype. Histopathology was performed using the PRETEXT (Pretreatment Extent) staging system developed by the International Society of Pediatric Oncology (SIOPEL). After the procedure, chemotherapy was initiated according to the standard protocol.

Keywords: epithelial hepatoblastoma, embryonic pattern, male infant, Beckwith-Wiedemann syndrome, rare disease, SIOPEL, management

Introduction

Hepatoblastoma is the most common primary malignant liver tumor in children, typically presenting within the first three years of life. Among its histological variants, the

epithelial subtype poses unique diagnostic and therapeutic considerations. The management of hepatoblastoma becomes even more complex when associated with congenital syndromes such as Beckwith-Wiedemann syndrome (BWS). BWS has classically been characterized by macroglossia, macrosomia, abdominal wall defects and an increased risk for embryonal tumors[1-4]. Surgical intervention remains the cornerstone of curative treatment, yet it is often challenged by tumor size, anatomical location, vascular involvement, and the delicate physiology of infants. Our case report highlights the modern surgical challenges encountered in the management of epithelial hepatoblastoma in an infant with BWS, underscoring the importance of multidisciplinary planning, technical precision, and individualized care strategies to optimize outcomes in this rare and demanding clinical scenario.

Case report

A 2-month-old male infant, born at term with a birth weight of 3.6 kg, previously clinically diagnosed with BWS syndrome based on macroglossia, left-sided hemihyperplasia, facial dysmorphic stigmatic features and neonatal hypoglycemia was referred to our department. On routine surveillance, due to abdominal tenderness and swelling, abdominal ultrasound revealed a large hepatic mass. An indication for imaging evaluation of the condition was considered, and a CT scan was ordered. The CT scan of abdominal cavity (Figure 1) showed two tumefactions located between the 5th and 6/7th liver segments, clearly demarcated with dimensions of 57 mm (larger lesion) and 33 mm (smaller lesion); the other intra-abdominal organs appeared normal. After the initial physical examination, clinical laboratory tests were taken into consideration. They showed elevated levels of lymphocytes, thrombocytes, DW-SV, and hyperglycemia as well. Thrombocytes were 675, glucose level 3.87, lymphocytosis75.9%. Based on the clinical presentation and symptoms, additional serum level markers were investigated. The levels of AFP were >1000.0 kiU/L (0-28 kiU/L). Laboratory evaluation showed markedly elevated AFP levels beyond age-adjusted reference ranges.

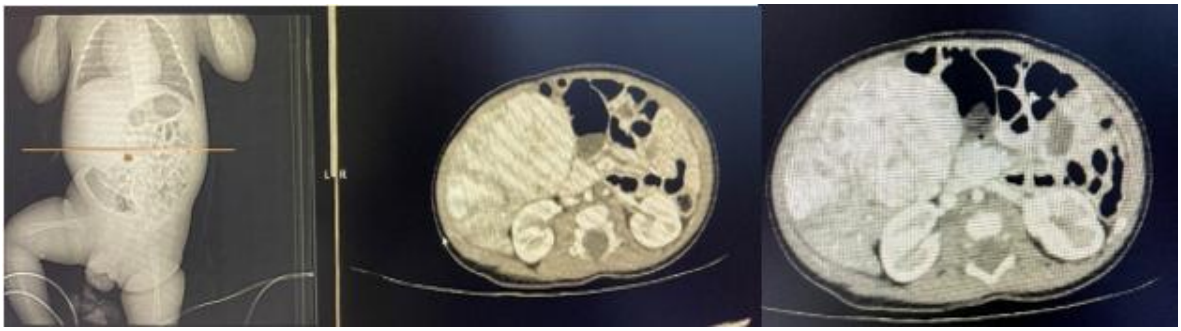

Fig. 1. CT scan of the patient showing two tumefactions

An urgent indication for surgical treatment was established. After anesthesiologic evaluation, preoperative preparation, and additional examinations, the child underwent surgical treatment. Under general endotracheal anesthesia (GETA), a right-sided laparotomy was made, and intraoperative findings revealed two large liver masses located in the right lobe (Figures 2 and 3). Cholecystectomy and right partial hepatectomy were performed, and the resected specimen was sent for histopathological verification (HP) (Figure 4).

Histopathology using the PRETEXT (Pretreatment Extent) staging system developed by the International Society of Pediatric Oncology (SIOPEL), confirmed the diagnosis of epithelial hepatoblastoma. In addition, immunohistochemical analysis was made, and demonstrated strong positivity for beta-Catenin, AFP, HepPar1, CEA, Glypican 3, CKAE1/AE3, CK7 INI, CK19, Ki67, Vimentin, LCA, supporting the diagnosis of embryonal

subtype – epithelial hepatoblastoma. (Figures 5, 6 and 7). Following the procedure, chemotherapy was initiated by a standard protocol and the child was referred to a pediatric hemato-oncologist for further treatment.

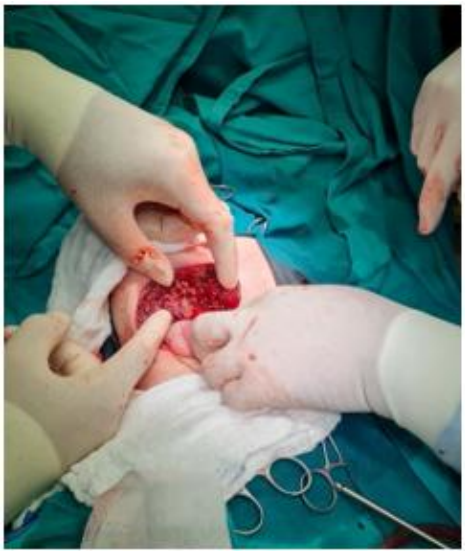

Fig. 2. Intraoperative finding

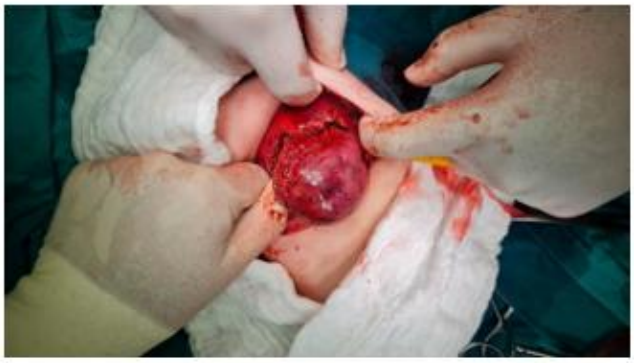

Fig. 3. Extirpation of the tumors

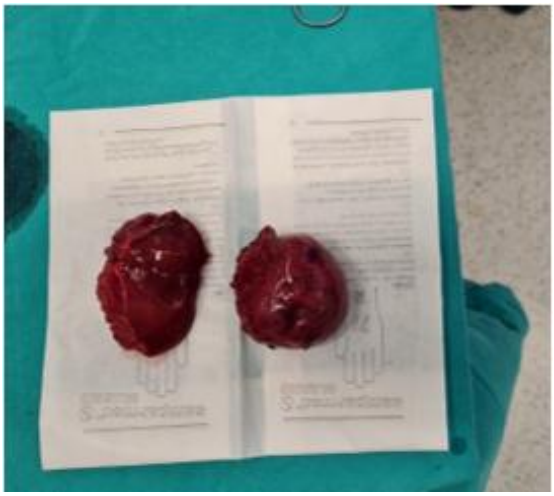

Fig. 4. Extirpated tumors

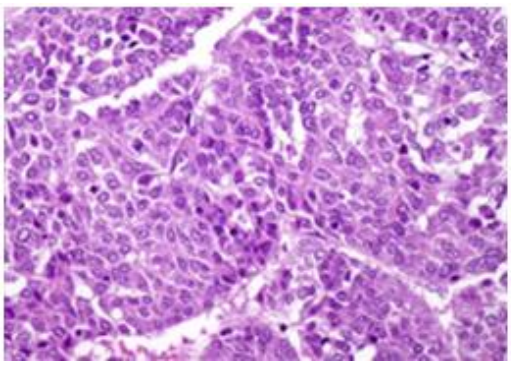

Fig. 5. Histopathology HEA specimen

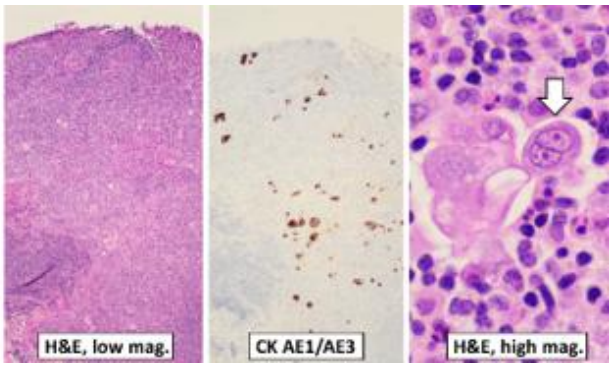

Fig. 6. C A1/AE3 Immunohistochemistry markers

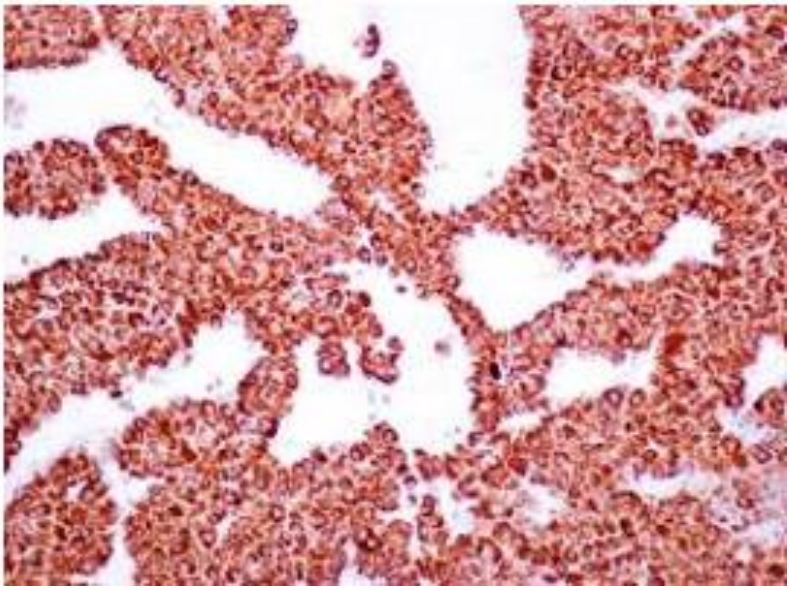

Fig. 7. HepPar-1 positive – immunohistochemistry marker

Discussion

Hepatoblastoma represents the most frequent malignant liver tumor in children worldwide, accounting for approximately two-thirds of pediatric liver cancers. It typically presents before the age of three and is often associated with elevated serum alpha-fetoprotein (AFP) levels. Histologically, hepatoblastoma is classified into epithelial and mixed epithelial-mesenchymal subtypes, with the epithelial variant being the most common. Advances in chemotherapy and surgical techniques have significantly improved survival rates, yet complete surgical resection remains the most critical determinant of long-term outcome. Challenges in management include tumor size, multifocality, vascular invasion, and the need for liver transplantation in unresectable cases. Patients with Beckwith-Wiedemann syndrome (BWS), an epigenetic imprinting disorder involving alterations in genes at the 11p15 chromosomal location, are predisposed to develop hepatoblastomas (HBs), which are rare embryonal liver tumors. Tumors can develop after a BWS diagnosis or conversely, can be presenting feature leading to a subsequent diagnosis. While HBs are the cardinal tumors of BWS, not all patients with the BWS spectrum will develop HBs[3]. The risk for HBs has been linked to the BWS population from early characterization and epidemiologic studies. Patients with BWS have a 2280 relative risk for HBs during the first four years of life compared to the general pediatric population, which appears to differ in association with the BWS molecular subtypes based on blood testing[3]. This association demonstrated an increased risk for WTs with IC1 GOM, leading to the hypothesis that IC1 alterations are more common in WTs. Children with BWS have a markedly increased risk of developing hepatoblastoma, necessitating vigilant surveillance with abdominal ultrasound and AFP monitoring during infancy and early childhood (Figure 8).

For BWSp, the overall tumor risk typically falls within the range of 8-12%. Among reported tumors, 47% are WT and 25% are HB. Neuroblastomas occur less frequently and are primarily seen in patients with CDKN1C PVs. The remaining tumor types are less common and do not meet the risk threshold for cancer surveillance. Individuals with IC1gain of methylation have the highest overall cancer risk at up to 28%, most commonly WT. Patients with pUPD11 have a risk range of 16-30%, most commonly for WT and HB. In patients with genome-wide paternal uniparental isodisomy, cancer risk is likely higher than in pUPD11, although these cases are too rare to define actual risk. These tumors also appear to occur later

in life than in pUPD11. Individuals with IC2 loss of methylation have an overall risk of 2-3% and most tumors reported are HB[5].

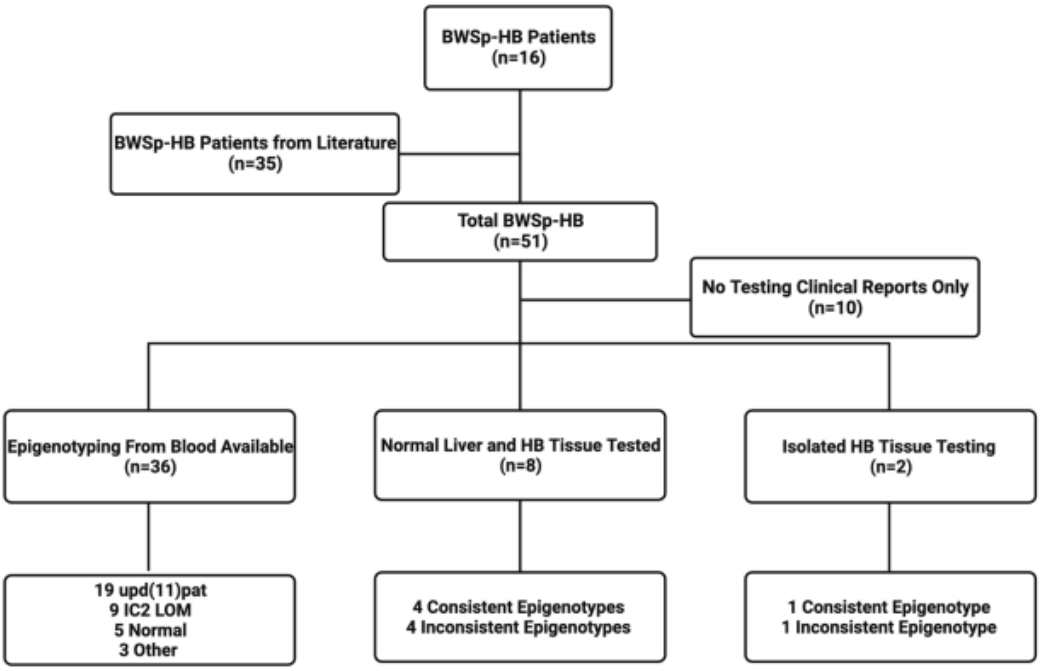

Fig. 8. Low sheet summarizing data collection for the BWS-HB study [3]

Trobaugh-Lotrario AD *et al.* (2014)[1] evaluated 56 patients, of median age at presentation with hepatoblastoma being 6 months. Thirteen of 26 patients were born prematurely. Of 31 evaluable patients, 19 exhibited hemihypertrophy; 32 of 33 patients with α-fetoprotein data reported had elevated levels at diagnosis. Overall survival was 75% (27 of 36 patients). Of 25 patients with data who survived, 24 were treated with chemotherapy and surgery (*vs*. only 2 of 8 who did not survive). All nine patients with hepatoblastoma detected by routine screening with outcomes reported were surviving at the time of the report. Overall survival was high in patients with BWS and hepatoblastoma, especially given lower stage at presentation and when treated with surgery and chemotherapy. Future prospective trials are needed to determine whether BWS is independently associated with outcome and whether routine screening improves the outcome.

The coexistence of BWS and hepatoblastoma presents unique challenges, as organomegaly and anatomical variations may complicate surgical planning and increase perioperative risks.

Modern surgical management of hepatoblastoma in infants with BWS requires balancing oncologic principles with the technical limitations imposed by patient age, tumor biology, and syndrome-related anomalies. Key challenges include:

- ***Tumor resectability****:* Large or centrally located tumors may necessitate complex resections or transplantation.
- ***Vascular involvement****:* Proximity to major hepatic vessels complicates safe dissection and margin clearance.
- ***Infant physiology****:* Limited blood volume and immature organ function heighten perioperative risks.
- ***Syndrome-specific factors****:* Macroglossia and organomegaly complicate airway management and perioperative care, while altered anatomy demands meticulous preoperative imaging and planning.

In our case, the experienced surgical team faced the dual challenge of achieving oncologic clearance while preserving sufficient hepatic parenchyma to sustain postoperative function. Advances in perioperative care, including improved anesthetic techniques and intraoperative monitoring, have contributed to safer outcomes, yet the margin for error remains narrow in this population. Optimal management of hepatoblastoma in the setting of BWS requires a multidisciplinary team involving pediatric surgeons, oncologists, anesthesiologists, geneticists, and radiologists.

Chemotherapy plays a critical role in downstaging tumors to facilitate resection, while liver transplantation remains a vital option for unresectable disease. Genetic counseling and long-term surveillance are equally important, given the ongoing risk of other embryonal tumors in BWS patients. Cisplatin-containing chemotherapy and complete surgical resection are both crucial in the cure of hepatoblastoma. Radical resection can be obtained either conventionally by partial hepatectomy or with orthotopic liver transplant, but the surgical approach to hepatoblastoma differs considerably across the world.[2] It is suggested that heroic liver resections with a high probability of leaving residual tumor should be avoided whenever possible. In such cases, primary orthotopic liver transplant should be considered[2].

This case highlights the importance of early detection through routine surveillance in infants with BWS. Regular abdominal ultrasound and AFP monitoring can identify hepatoblastoma at a stage when surgical resection is more feasible. Furthermore, it emphasizes the need for individualized surgical strategies that balance oncologic principles with the unique physiological and anatomical challenges posed by syndromic infants.

Conclusion

Pediatric liver cancers (PLCs) are rare and account for only 1-2% of all pediatric malignancies. Of these, the most frequent tumor is hepatoblastoma (HB), which affects mainly young infants before the age of 5 years. While HB is mostly sporadic, 15% of HB cases are associated with a predisposition syndrome such as familial adenomatous polyposis (FAP), trisomy 18, Simpson-Golabi-Behmel syndrome or Beckwith Wiedemann syndrome (BWS), and an overgrowth syndrome caused by a genetic or epigenetic alteration at locus 11p15.5. [6] Despite being the most common liver cancer in children, hepatoblastoma (HB) is a rare neoplasm. Consequently, few pretreatment tumors have been molecularly profiled, and there are no validated prognostic or therapeutic biomarkers of HB patients[7].

Most cases of BWS are mosaic and clinical features typically vary between patients with rare familial forms identified. Many cases of isolated hemihyperplasia (IHH) are considered a more subtle presentation of BWS, leading to a spectrum of features resulting from a variety of structural, genetic or epigenetic abnormalities localized to chromosome 11, termed the “11p overgrowth spectrum“. The incidence of BWS is 1 in 10,500 births, but with the inclusion of subtle cases with IHH, the true incidence is likely higher. BWS is caused by dysregulation of growth-related genes encoding both proteins and regulatory RNAs (H19, IGF2 and CDKN1C) on chromosome 11p15 that are imprinted and are therefore normally expressed in a parent-of-origin- specific manner[8].

The management of epithelial hepatoblastoma in infants with BWS exemplifies the complexity of modern pediatric oncology surgery. Successful outcomes hinge on early diagnosis, careful preoperative planning, and a multidisciplinary approach tailored to the patient’s unique syndromic context. This case reinforces the necessity of vigilant surveillance in BWS and highlights the evolving role of surgical innovation in overcoming the challenges of treating rare but high-risk pediatric tumors. Children with BWS are predisposed to hepatoblastoma, with tumor risk varying depending on the molecular subtype of BWS. For example, patients with IC1 gain of methylation have a tumor risk approaching 23-29%, while those with paternal uniparental isodisomy (pUPD) carry an intermediate risk of 14-17%.

Surveillance protocols recommend serial abdominal ultrasound and serum alpha-fetoprotein (AFP) monitoring every 2-3 months until the age of 4 years, which has proven effective in detecting tumors at earlier, more resectable stages.

Complete surgical resection remains the cornerstone of cure in hepatoblastoma. However, infants with BWS present unique anatomical and physiological challenges. In some cases, neoadjuvant chemotherapy is essential to downstage tumors, improving the feasibility of surgical resection. For unresectable disease, liver transplantation remains a vital option and has shown favorable long-term outcomes in carefully selected patients. Optimal management requires a multidisciplinary team including pediatric surgeons, oncologists, anesthesiologists, geneticists, and radiologists. Genetic counseling is critical for families, as recurrence risk and predisposition to other embryonic tumors (e.g., Wilms tumor) remain high. Long-term follow-up is necessary to monitor for late effects of chemotherapy and to continue tumor surveillance.

This case emphasizes the importance of early detection through vigilant surveillance in infants with BWS. Early diagnosis allows for timely surgical intervention, which is the most significant determinant of survival. Furthermore, it highlights the need for individualized surgical strategies that balance oncologic clearance with preservation of hepatic function.

Conflict of interest statement. None declared.

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