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Hepatoblastoma: A Case Report

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Abstract

Hepatoblastoma is a rare type of pediatric malignant disease and represents the most frequent cause of liver tumors during childhood. We describe the diagnosis and treatment of a 14-month-old female patient who presented with abdominal swelling, anorexia, and weight loss. Initial investigations indicated elevated alpha-fetoprotein levels and thrombocytosis. A CT scan showed a heterogeneous mass arising in the right lobe of the liver. Histology revealed hepatoblastoma, epithelial type, and fetal pattern. The patient was treated as a standard risk according to the Pretext classification (Pretext I-III) with neoadjuvant Cisplatin (4 cycles) following the SIOPEL 3 protocol, resulting in a 40% reduction in tumor size and a successful partial hepatectomy.

Keywords

Hepatoblastoma, Liver Tumor, Hepatectomy

Introduction

Liver tumors comprise between 1-2% of all pediatric tumors [1]. They are a heterogeneous group of epithelial and mesenchymal neoplasms, rare in childhood, with a global incidence of 1.8 million people per year [1,2]. Hepatoblastoma (HB), hepatocellular carcinoma (HCC), and embryonal sarcoma (ES) are the three most common liver tumors in children and adolescents. It has been estimated that HB accounts for over 90% of primary hepatic malignancies among children less than 3 years of age [1,2]. It occurs predominantly in a unifocal manner in the right liver lobe, but it can be multifocal and develop in all liver segments. HB affects white children more than black children and is more common in boys than girls [1,2].

A well-developed HB may mimic HCC. Hematogenous lymph nodal metastases have been reported [2,3]. Several conditions are associated with HB, including Beckwith-Wiedemann syndrome, familial adenomatous polyposis, and hemihypertrophy [2-4]. Premature children with low birth weight and very low weight have a significantly higher rate of HB [4]. Surgery remains the mainstay of treatment for HB, and complete resection is the only way to achieve a cure [3,4].

When patients have a partial hepatectomy, the 5-year overall survival (OS) rate for HB can reach 91% [4]. A good prognosis is expected if HB is fully resectable due to its good response to adjuvant chemotherapy. Conversely, incomplete removal due to late diagnosis yields less favorable results because HB cells develop resistance to cytostatics after repeated chemotherapy, limiting therapeutic success [2-4]. Black patients tend to have poorer outcomes [4,5].

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The Children's Hepatic Tumors International Collaboration (CHIC), consisting of leadership from the four major cooperative trial groups (the International Childhood Liver Tumours Strategy Group, Children's Oncology Group, the German Society for Paediatric Oncology and Haematology, and the Japanese Study Group for Paediatric Liver Tumours), created a shared international database that includes comprehensive data from 1,605 children treated in eight multicenter hepatoblastoma trials over 25 years [6,7]. The findings revealed that children under 3 years old with alpha-fetoprotein (AFP) < 100 ng/ml, the pre-treatment extent of tumor (PRETEXT) group, and the PRETEXT annotation factors—metastasis (M), macrovascular involvement of all hepatic veins (V) or portal bifurcation (P), contiguous extrahepatic tumor (E), multifocal tumor (F), and spontaneous rupture (R)—were found to be the most prognostic diagnostic factors at initial analysis [7].

The treatment regimens carry a risk of toxicities, including cisplatin-induced ototoxicity and nephrotoxicity, doxorubicin-induced cardiomyopathy, and secondary leukemia [8]. In patients treated for HB with 600 mg/m^2 of cumulative cisplatin, hearing loss to the point of requiring augmentation devices occurs in half of all patients, severely impacting childhood development and quality of life [8]. The management of patients with HB has traditionally varied among countries. Studies in HB have previously been conducted by the four main pediatric oncology consortia, namely the Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL) in Europe, the Children's Oncology Group (COG) in North America, the Japanese Study Group for Paediatric Tumours (JPLT), and the German Society for Paediatric Oncology and Haematology (GPOH). In Europe, chemotherapy before surgery was recommended for all patients, whereas in the USA, tumor resection followed by chemotherapy was allowed only if the tumor met strict resection criteria. The Paediatric Hepatic International Tumour Trial (PHITT), the international collaboration of North American, European, and Japanese pediatric oncology groups, aims to unify risk stratification and treatment protocols [8,9].

Case Presentation

A 14-month-old female patient was admitted to the pediatric ward presenting with abdominal swelling persisting for 3 months, poor appetite, and weight loss. The patient's birth weight was 2,800 grams after 38 weeks of amenorrhea.

Clinical Examination Findings:

A distended abdomen was noted during a physical examination, along with a palpable mass in the right hypochondrium that was non-painful upon palpation, with ill-defined borders. No other abnormalities were identified during the physical examination.

Evaluation of Laboratory Tests:

Initial investigations revealed thrombocytosis of 1215 × 10^9/L and an elevated AFP of 2,671.49 ng/ml. Hepatitis B surface antigen and anti-hepatitis C tests were negative.

Imaging Evaluation:

An abdominal ultrasound identified a large heterogeneous mass located in the right lobe of the liver, characterized by cystic regions and calcifications, measuring 12 × 10 × 10 cm. A contrast-enhanced axial CT scan of the abdomen revealed a large circumscribed heterogeneously enhancing mass, comprising soft tissue, fluid densities suggestive of hemorrhage, and a few coarse calcifications, measuring 13 × 10 × 10 cm. This mass occupied and distended the upper abdomen, exerting pressure on adjacent viscera (**Fig-1A** and **Fig-1B**). A biopsy was conducted, and the findings indicated hepatoblastoma of the epithelial type with a fetal pattern.

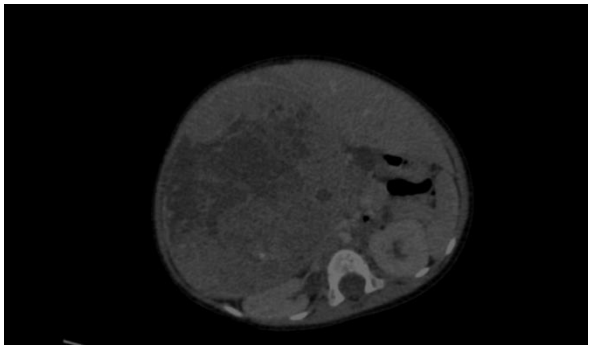

Fig-1A:

A Contrast-enhanced CT scan showed a large circumscribed heterogeneously mass; It measures 13x10x10 cm.

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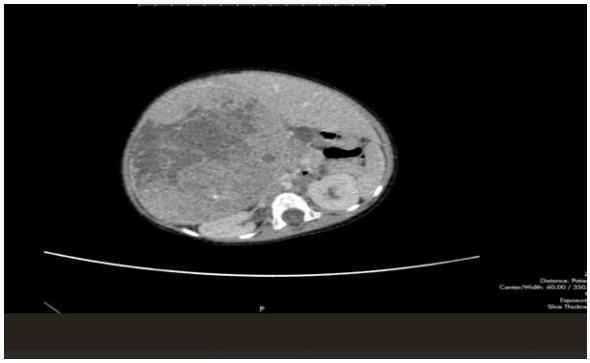

Fig-1B:

A Contrast-enhanced CT scan revealed a large mass consisting of soft tissue, fluid densities like hemorrhage or necrosis, and a few calcifications.

Treatment

The patient was treated according to the SIOPEL cooperative group and classified as having standard-risk HB (PRETEXT III staging and alpha-fetoprotein >100 ng/ml; SR-HB). The patient received neoadjuvant chemotherapy according to the SIOPEL-3 protocol with Cisplatin (CDDP) 80 mg per square meter of body surface area, administered every 14 days. After 4 cycles of neoadjuvant chemotherapy, a CT scan indicated a reduction of more than 40% in the tumor size (**Fig-2**). There was a clinical improvement in the patient's initial symptoms, with normal platelet levels, although AFP levels remained elevated. Subsequently, a partial hepatectomy was performed, resulting in the complete resection of the liver tumor. The patient then underwent 2 cycles of adjuvant chemotherapy with CDDP. The final evaluation confirmed complete remission.

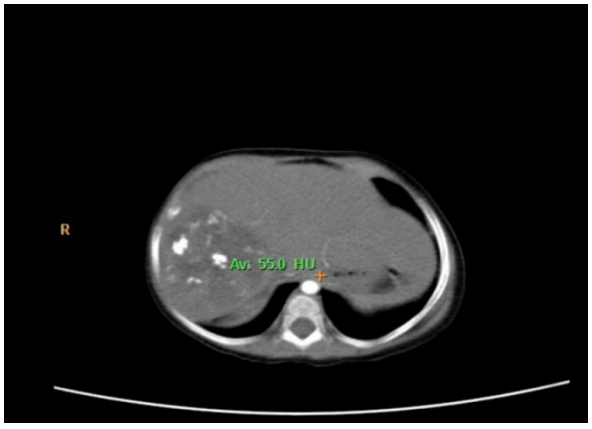

Fig-2:

A Computed axial tomography with intravenous contrast showing a well-defined heterogeneous mass, with areas of central necrosis and coarse calcifications measuring 6.3x 6,5x 7,5 cm.

Discussion

Hepatoblastoma (HB) is the third most prevalent abdominal malignancy in children, typically diagnosed at a median age of 19 months, with 5% of cases occurring in children over 4 years old, and a higher incidence in males [10]. HB develops from degenerated hepatoblasts and can be differentiated according to the various stages of liver development [10].

HB is categorized according to the original histological classification by Ishak and Glunz [3,4,8]. Histologically, HB is broadly classified into two main types: epithelial and mixed. Depending on the degree of differentiation, HB cells can be further classified into two subtypes: embryonic and fetal. In some instances, both cell types may be present. Embryonic tumor cells are less differentiated, while fetal cells are well-differentiated [3,8]. Small-cell anaplastic HB is a unique subtype [8]; it mainly infiltrates the bile ducts and is considered prognostically unfavorable. In addition to epithelial components, the mixed HB type contains mesenchymal stroma such as osteoid, collagen fibers, and, rarely, cartilage and skeletal muscle cells.

Liver progenitor cells have the ability to express keratin 19 (CK19) and/or the epithelial cell adhesion molecule (EpCAM) [18–21]. EpCAM is a transmembrane glycoprotein mediating calcium-independent homotypic cell-cell adhesion in the epithelium. This molecule is also involved in cellular signaling, migration, proliferation, and differentiation. It impacts the event-free survival outcome of patients with HB. CK19 expression is linked to aggressive behavior in HB and HCC. HB is a genetically simple cancer with an average of 3.4 mutations per tumor [8,9,11]. The most common alteration in HB, with an incidence of 48-67%, is a mutation of the beta-catenin gene (CTNNB1), either through point mutation or deletion, mainly affecting exon 3 [11]. This leads to the accumulation of CTNNB1 in the nucleus and the constitutive activation of the oncogenic Wnt signaling pathway. Apart from CTNNB1, only two other recurring mutations have been identified in HB through whole-exome sequencing, namely mutations of the nuclear factor erythroid-derived 2-like 2 (NFE2L2) gene in 5-9% of cases and the telomerase reverse transcriptase (TERT) promoter in

2-4% of cases [11,12].

Although imaging tools are crucial for diagnosing HB, only a biopsy can confirm the diagnosis. A biopsy is necessary for children under 6 months old and over 3 years of age due to the possibility of various tumors. A high AFP level may be attributed to the age of the child, helping to differentiate between HB and HCC in older children [3,4,11]. According to the German Society for Pediatric Oncology and Hematology (GPOH) guidelines, for children between the ages of 6 months and 3 years with a suspected liver tumor and an AFP value over 1,000 ng/ml, or at least three times higher than the age norm, a biopsy confirming the diagnosis of HB is not necessary, especially since in these cases, the incriminated liver tumor is always HB [11,12]. However, this view is not universally accepted; on the contrary, most oncologists require a tumor biopsy to confirm the diagnosis [13].

Biopsy tissue can be obtained through percutaneous core, laparoscopic core wedge, or open biopsies, depending on the balance between the risk of bleeding and acquiring enough of the target tissue. It's recommended to obtain five cores of the tumor and one core of normal liver, or at least three cores for pathological examination [13-15]. As staging systems (PRETEXT, COG, etc.) and risk stratification have matured in recent years, the histological subtype has gained great importance in formulating treatment protocols [15,16]. Not only the histological subtype but also the results of immunohistochemical testing could guide chemotherapy algorithms [16]. The clinical significance revealed by immunohistochemistry varies considerably. For example, integrase interactor 1 (INI 1) negative epithelial HB with a low serum AFP level may suggest a rhabdoid-originated tumor and receive a compromised chemotherapy regimen. Comparisons between PRETEXT stage I/II and stage III/IV have shown that CD44 is more highly expressed in the latter stages. Abnormal expressions of CD90, CD133, and CD40 are associated with disease progression [14-16].

If a liver tumor is suspected, the first step is to conduct contrast-enhanced sonography of the liver. If the tumor shows increased echogenicity on contrast-enhanced sonography and pronounced vascular supply on Doppler ultrasound, possible tumor invasion into one or more hepatic vessels is suspected [16,17]. This indicates a malignant process; however, these findings are not confirmatory evidence of malignancy. Other imaging options, namely magnetic resonance imaging (MRI) or computed tomography (CT) of the abdomen with contrast agent, can not only provide evidence of a malignant tumor of the liver but also allow for the assessment of the extent of malignancy, including the relationship of the neoplasm to the hepatic vessels and liver segments [15-17].

Nevertheless, a reliable diagnosis of HB cannot be achieved with these examinations alone. However, thanks to these techniques, angiography or liver scintigraphy can now be used [17]. A lung CT scan to determine or exclude lung metastases and skeletal scintigraphy with 99-technetium phosphonate to detect or exclude possible bone metastases is recommended as a precautionary measure [16,17]. It remains to be seen whether FDG-PET/CT performed for the initial diagnosis of a possible hepatoblastoma is sensible, especially since only a possible correlation between uptake and tumor-related increased AFP values can be established. It is well known that FDG-PET/CT is vital during treatment or as part of the follow-up for a malignant tumor. For example, in HB, the detection of metabolically active metastases indicates an unfavorable prognosis [16,17].

The first risk-stratifying system was the pre-treatment extent of the tumor system (PRETEXT), reported by SIOPEL in 1992 [18]. Evan's risk stratification was adopted by the Children's Oncology Group (COG), and the stratification was based on initial surgery. With advances in imaging techniques, the PRETEXT system has become a hybrid applied in serial trials conducted by international cooperative groups. In 2017, four international cooperative groups (SIOPEL, COG, JPLT, GPOH) collaborated to write a new staging system, CHIC-HS [18]. CHIC-HS is a stratification based on the PRETEXT system and is being used in an ongoing hepatoblastoma trial. The PRETEXT system includes content concerning standardized imaging evaluation. In 2017, these organizations created a common set of definitions to be used in future trials [18,19].

The current therapeutic approach involves three treatment options: (1) pre-and/or post-operative chemotherapy, (2) tumorectomy with possible partial liver resection, and (3) liver transplantation. The use of chemotherapies, including platinum compounds for neoadjuvant and adjuvant treatment of hepatoblastomas, has resulted in a significant improvement in outcomes [10,13,14].

Studies in HB have previously been conducted by the four main pediatric oncology consortia [10,13,14]. SIOPEL-1 established the efficacy of cisplatin/doxorubicin (PLADO) combination therapy in HB. The 5-year event-free survival (EFS) was 66% (95% CI 59-74%), and the overall survival (OS) was 75% (95% CI 68-82%) [12]. This trial also validated the pre-treatment extent of the tumor (PRETEXT) staging system [20].

SIOPEL-2 (1994-98) stratified patients into two groups: standard-risk (SR) patients with tumors confined to the liver and involving no more than three hepatic sectors, and high-risk (HR) patients with HB extending into all four sectors and/or with lung metastases or intra-abdominal extrahepatic spread [12]. SR-HB patients were treated with four courses of cisplatin monotherapy (CDDP 80 mg/m^2) every 14 days, delayed surgery, and then two more CDDP courses. HR-HB patients were given CDDP alternating every 14 days with carboplatin (CARBO) 500 mg/m^2, and doxorubicin (DOXO) 60 mg/m^2. For SR-HB patients, 3-year OS and PFS were 91% and 89%, respectively, suggesting that cisplatin alone was sufficient to treat this group [20].

SIOPEL-3 (1998-2006) compared CDDP monotherapy and CDDP/DOXO (PLADO) in SR-HB patients in a prospective randomized trial. Three-year EFS and OS were similar in both groups: 83% (95% CI 77 to 90) and 95% (95% CI 91 to 99) in the cisplatin group, and 85% (95% CI 79 to 92) and 93% (95% CI 88 to 98) in the PLADO group. Thus, cisplatin monotherapy was shown to be sufficient in treating patients with SR-HB [20].

SIOPEL-4 (2005-09) was a prospective study in patients with HR-HB, involving further intensification of platinum chemotherapy administered weekly in combination with doxorubicin, followed by surgical resection of all remaining tumor lesions if feasible [20].

The COG in North America initially favored a postoperative chemotherapy regimen based on Evans' classification. COG INT-0098 (1989-92) was a randomized trial comparing two regimens known to be effective in HB: cisplatin, vincristine, fluorouracil (C5V), and PLADO. Five-year EFS estimates were 57% (SD = 5%) and 69% (SD = 5%) for patients on C5V and PLADO, respectively (P = 0.09). Toxicities were greater with PLADO, including 2 toxic deaths. Therefore, C5V was adopted as the preferred regimen for treating HB [10,14,20].

In the COG trial, AHEP0731, patients with stage I PFH are classified as very low risk and treated with resection only. Patients with stage I and II SCU histology and all stage III patients are classified as intermediate risk and receive 6 cycles of C5V plus doxorubicin (C5VD) in total, with surgery after either 2 or 4 cycles of chemotherapy [10,14,20].

Surgery remains the most vital treatment for curing HB. The timing of surgical resection of HB varies among collaborative groups [15,21]. SIOPEL recommends preoperative neoadjuvant chemotherapy for all staged children to reduce the extent of hepatic resection, avoid aggressive surgery, and minimize surgical trauma. In the COG, GPOH, and JPLT studies, an upfront resection strategy was adopted for patients with PRETEXT I/II. According to the COG study, pure fetal hepatoblastoma with PRETEXT I can be cured with radical surgery [10,15,21]. The COG surgical guidelines recommend segmental or lobectomy for children with PRETEXT stages I and II, lobectomy or trilobectomy for children with PRETEXT stages II and III without involvement of large vessels, and complex hepatectomy or liver transplantation for children with PRETEXT stages III and IV with involvement of large vessels. These cases should be assessed by an experienced team with expertise in liver transplantation [10,13,15,21]. Although the protocols used by the various collaborative groups differed, the outcomes were generally similar [10,15,21].

This patient was evaluated according to the SIOPEL

cooperative group with neoadjuvant chemotherapy according to SIOPEL-3, resulting in a good response that led to partial hepatectomy and then continued with 2 adjuvant cycles of CDDP. The patient exhibited a significant response to chemotherapy from the first cycle, despite elevated levels of AFP. Some authors have suggested that a low decline in AFP levels after the first cycle of chemotherapy and increased AFP levels preoperatively and postoperatively are significantly linked to treatment failure [22,23]. In this instance, the patient had a favorable outcome and is currently in remission.

Conclusions

HB is a rare type of children's liver tumor. A multidisciplinary evaluation is crucial to improving the patient's outcome. This case describes a good response to neoadjuvant chemotherapy and partial hepatectomy with complete remission.

Consent to publish the case report was not obtained. However, this report does not contain any personal information that could lead to the identification of the patient.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

Author Contributions

Abel Ning Caballero was responsible for the conceptualization, investigation, and writing of the original draft, as well as the visualization and review & editing of the manuscript. Kandecy Archer contributed to the critical review and visualization aspects of the manuscript. All authors approved the final version of the manuscript.

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