Hepatoblastoma in A 19-Year-Old Girl:
A Rare Case Report and Review of The Literature

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ABSTRACT

Hepatoblastoma is a rare malignant tumor in children that only accounts for approximately 1% of pediatric cancers, but the most frequent liver tumor among children. It’s an uncommon malignancy in adult with a very poor prognosis. No therapeutic strategy has been established. The cornerstone of treatment was the liver resection, but recurrence is common even after complete resection. In this paper, we present a rare case of hepatoblastoma in a young adult female with a review of the literature.

Keywords: hepatoblastoma, liver tumors, young adult

1. INTRODUCTION

Hepatoblastoma (HB) is a rare malignant tumor in children that only accounts for approximately 1% of pediatric cancers [1]; Otherwise, it’s the most common liver tumor in children and usually occurs under the age of 2 years [2], a review of SEER database for the 2002–2008 period demonstrates that among patients younger than 5 years, hepatoblastoma accounts for 91% of primary hepatic malignancy cases. HB in adults is extremely rare, with no more than 70 cases reported in the medical literature till date [3] and no effective diagnostic and therapeutic strategy has been established. The 5-year overall survival rate in children with not disseminated tumors is close to 70% [4,5,6,7]. In contrast, adult hepatoblastoma has a fatal prognosis, with a mean survival time of two months and one-year survival of 24% [8,9]. Alpha-fetoprotein (AFP) is a useful clinical marker for diagnosing hepatoblastoma, but approximately 10% of patients do not present with an elevated AFP level at the time of diagnosis [10]. AFP was also found to play a significant role in the patient prognosis [11]. In this paper, we present a rare case of hepatoblastoma in a young adult female.
2. CASE PRESENTATION

A 19-year-old white female was referred to our hospital, with a 4-month history of abdominal pain and a palpable mass in right hypochondrium, without other symptoms. The patient was previously healthy with no use of contraceptives. Physical examination found a palpable hepatomegaly of 4 cm below the costal border, without a splenomegaly or ascites. Laboratory studies showed: AFP: 1.2x10^5 ng/ml. Abdominal CT scan revealed a large mass measuring 25 x 22 cm in the right lobe of liver. Needle biopsy was performed and hepatoblastoma was proposed by the pathologist. The patient was staged PRETEXT IV and received a preoperative chemotherapy based on alternating cycles of cisplatin and the combination of carboplatin plus doxorubicin, then a surgery was performed with an atypical resection. A complete resection of a mass measuring 19x13 cm was possible with tumor freed margins. A post-operative chemotherapy was delivered. No major incident was noted. Three month later the patient complained of an abdominal enlargement, the CT scan showed two hypodense masses with heterogenous enhancement, localized in segments 2 and 8 suggesting a local relapse, measuring 6.7 cm and 6.4 cm suggesting a local recurrence, with an abdominal wall metastasis measuring 5.1 cm (Rectus Abdominis muscle) (figure 1), and two metastatic nodules in the lung (figure 2). The patient was considered inoperable. One week later the patient presented to emergencies with convulsive seizures and loss of consciousness. She was admitted to intensive care in a coma. A CT scan showed a brain metastasis. Few days later the patient died from brain progression.

Figure 1: Abdominal CT scan with contrast, showing two hypodense masses with heterogenous enhancement, localized in segments 2 and 8 suggesting a local relapse, associated with abdominal wall metastasis.
Hepatoblastoma is a malignant embryonal tumor that is the most frequent liver tumor among children [12]. Approximately 90% of the cases occur in patients under 5 years of age and two thirds of the cases occurs in the 2 years of life [13], it’s an uncommon malignancy in adult. The first case of an adult hepatoblastoma was described in 1958 [14]. Patients with hepatoblastoma commonly present with an abdominal mass with mild abdominal pain associated with weight loss. The serum level of AFP is increased in 90% of cases, at a threshold greater than $1.1 \times 10^4$ ng/mL [15,16]. The evolution of the AFP level is an important prognostic factor to consider; an early decreasing greater than 1 log during the preoperative treatment phase is an indicator of survival without events [17]. Instead, in the rare case of infants with hepatoblastoma with normal AFP, the prognosis is very poor [18]. The lung is the most common site of metastasis [19]. The risk of metastasis is higher among adult patients with hepatoblastoma than in young infants [20]. Huang et al. [21] reported a case of metastatic hepatoblastoma in the right ventricle in an 18-year-old boy.

**Figure 2: Chest CT scan with contrast, showing two metastatic nodules in the lung**

3. **DISCUSSION**

Hepatoblastoma is a malignant embryonal tumor that is the most frequent liver tumor among children [12]. Approximately 90% of the cases occur in patients under 5 years of age and two thirds of the cases occurs in the 2 years of life [13], it’s an uncommon malignancy in adult. The first case of an adult hepatoblastoma was described in 1958 [14]. Patients with hepatoblastoma commonly present with an abdominal mass with mild abdominal pain associated with weight loss. The serum level of AFP is increased in 90% of cases, at a threshold greater than $1.1 \times 10^4$ ng/mL [15,16]. The evolution of the AFP level is an important prognostic factor to consider; an early decreasing greater than 1 log during the preoperative treatment phase is an indicator of survival without events [17]. Instead, in the rare case of infants with hepatoblastoma with normal AFP, the prognosis is very poor [18]. The lung is the most common site of metastasis [19]. The risk of metastasis is higher among adult patients with hepatoblastoma than in young infants [20]. Huang et al. [21] reported a case of metastatic hepatoblastoma in the right ventricle in an 18-year-old boy.

HB is believed to arise from a hepatic blastema, but this hypothesis seems to be inapplicable to adult hepatoblastoma [22]. It may occur in association with genetic disorders, Weber et al. screened 34 hepatoblastoma tumors, the results identified gains on chromosomes 1q and 2 as the hallmark of DNA copy number changes in hepatoblastoma, 2q24 being a critical chromosomal band; this study also provided evidence that gains on 8q and 20 may play a role as markers of prognostic significance in hepatoblastoma [23]. Several signaling pathways, whether or not involved in liver development, have been identified. The WNT / beta-catenin signaling pathway involved in hepatic development and regeneration as well as in tumorigenesis is activated in more than 90% of HB cases [24]. A higher presence of beta-Catenin in the cellular nuclei has been described in the less differentiated tumors and associated with a poorer outcome [25].

Even if the diagnosis of HB is highly probable on the association of a liver tumor with an increase in AFP level above 104 ng/mL, the biopsy is essential not only to confirm the diagnosis but specially to clarify the biology of the tumor, and allow better stratification of patients before any treatment. Harada et al. insisted on the importance of needle aspiration biopsy to diagnose hepatoblastoma preoperatively [26].

The diagnosis of HB is mainly based on histology. In 1967, Ishak and Glunz [27], proposed two HB subtypes: (1) epithelial, (2) mixed epithelial and mesenchymal. Epithelial type consists of fetal and embryonic cells presenting alone or in combination. A more aggressive macrotrabecular pattern, and the small cell undifferentiated subtype were recognized later [28,29]. Not all of these conventionally accepted characteristics are found in adult lesions. In pediatrics, histology is commonly accepted to have a prognostic value and, as such, plays a key role in the determination of the therapeutic regimen.

Based on review of the literature by Rougemont et al. [8] there is no standardized management of adult HB. There are two different strategies regarding the treatment of pediatric HB. The North American groups support immediate surgery for localized tumors [30,31], whereas Europe favors preoperative chemotherapy in all cases, followed by surgery. Between 1990 and 1994, the Society of Pediatric Oncology Liver Tumor Study Group launched its first prospective trial (SIOPEL-1) with the intention to treat all patients with preoperative chemotherapy and delayed surgical resection. This study revealed that preoperative chemotherapy (cisplatin and doxorubicin) seems to make tumor resection easier [32]. The tumor is classified according to PRETEXT (pretreatment extent of disease) or POST-TEXT (post treatment extent of disease) based on the anatomy of the liver and radiological findings at diagnosis, to try to predict resectability and outcome. The treatment of pediatric hepatoblastoma has markedly improved over the past decades and many patients can expect long-term survival at present. In the SIOPEL-2 study patient were divided in two groups [33]. The ‘standard risk’ group (SR-HB) included patients with tumors involving no more than three hepatic sectors and without evidence of extrahepatic disease, and the ‘high risk’ group (HR-HB) (of treatment failure) included patients with tumors involving all four hepatic sectors and/or with evidence of extrahepatic disease. Standard risk patients were treated with cisplatin alone in order to avoid the potential cardiotoxicity associated with doxorubicin, whereas high risk patients were treated with the combination of cisplatin/doxorubicin/carmustine. The response rates for the entire SR-HB and HR-HB groups were 90% (95% CI 80–96%) and 78% (95% CI 65–87%), and resection rates were 97% (95% CI 87–99%) and 67% (95% CI 54–79%) including several children undergoing liver transplantation. For SR-HB patients, 3-year overall survival (OS) and progression-free survivals (PFS) were 91% (+/- 7%) and 89% (+/- 7%) and for the HR-HB group 53% (+/- 13%) and 48% (+/- 13%), respectively. A treatment strategy based on CDDP monotherapy and surgery thus appears effective in SR-HB but, despite CT intensification, only half of the HR-HB patients are long-term survivors.

To improve the survival of patients with bad prognosis, the SIOPEL group decided to intensify chemotherapy with use of aggressive surgery (including orthotopic liver transplantation) in the subsequent studies. In the SIOPEL-3 the results represented an improvement. The PFS and OS estimated at 3 years were 65% (95% CI, 57% to 73%) and 69% (95% CI, 62% to 77%) for high risk [35]. In the SIOPEL-4 the regimen used in this study aimed to further intensify chemotherapy in children with high-risk HB by adopting a weekly dose dense administration of cisplatin in combination with monthly doxorubicin and delayed radical surgery. As a single-arm trial, SIOPEL-4 was not randomized, but outcomes were far superior to historical controls [37]. In contrast, adult hepatoblastoma has an extremely poor prognosis. Despite many scientific publications so far, no randomized studies have been conducted,
only single cases or small series were reported. A review of the literature by Celotti et al. [37] in 2016 revealed only 58 reports, with 63 patients. An overall survival analysis was performed, considering 43 cases in which follow-up data were available. Overall survival was very poor: median survival time in the Kaplan-Meier curve was 5 months with a 1-year survival rate that was near 30%. The cornerstone of treatment for HB was the liver resection. Surgery patients presented improved survival with statistical significance, compared to patients who underwent other treatments or no-treatment (P < 0.0001). 1-year survival was 60%. Neoadjuvant and adjuvant treatments such as chemotherapy, transarterial chemoembolization (TACE) or radiotherapy were described for advanced HB, or when recurrence occurs. Drugs employed, chemotherapy/ TACE protocols were different in every report.

4. CONCLUSION

The very low incidence of HB outside of infancy and non-specific initial symptoms make the diagnosis difficult, it’s usually diagnosed at an advanced stage. Although epidemiologic studies have been initiated to investigate risk factors for HB in infants, the influence of older age at diagnosis on disease course and survival has not been well studied. HB in adult patients remains a very aggressive malignancy with poor prognosis compared to childhood patients. Current literature for treatment of adult HB is insufficient. Therefore, further research is needed to provide optimal treatment strategies. Adult HB may well be classified according to the PRETEXT score and treated according to the SIOPEL protocols, meanwhile multidisciplinary efforts are needed, and optimal treatment modalities still remain to be defined to improve patients’ outcomes.

REFERENCES

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