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HEPATOBLASTOMA PRODUCING HUMAN CHORIONIC BETA GONADROTOPIN (B-HCG): A CASE REPORT

Yulla Fagundes Severino

Abstract: **Introduction:** Hepatoblastoma (HB) is the most common liver tumor in infants and children. It is responsible for more than 90% of malignant liver tumors among children under 5 years of age. HB, in most cases, is associated with an increase in AFP, but there is another marker, human chorionic gonadrotophin beta (B-hCG), little described in the literature because its occurrence is rare, since only 18% of cases have it. a high level of B-hCG. Objective: To report the case of a patient diagnosed with hepatoblastoma who at the time of diagnosis had high serum levels of alpha-fetoprotein (AFP) and B-hCG. **Description of case:** This is a case in which a patient aged 1 year and 3 months was diagnosed with B-hCG-producing hepatoblastoma with high levels of AFP. He underwent preoperative chemotherapy, total tumor resection and postoperative chemotherapy and is in remission. **Discussion:** Clinically, hepatoblastoma appears similar to other liver tumors, with abdominal distention or a palpable abdominal mass, often associated with nonspecific symptoms such as the anorexia, pain, fatigue and weight loss. Since this is a rare case, it is very important to document new cases to enrich the literature on the subject.
Keywords: Hepatoblastoma. Alphafetoprotein. B-hCG.

INTRODUCTION

Hepatoblastoma (HB) is an embryonic malignant tumor with different patterns of differentiation and the most common liver tumor in infants and children. It accounts for more than 90% of malignant liver tumors among children under 5 years of age (Towbin, A.J. et al., 2018).

The etiology of hepatoblastoma is still unknown, but there are descriptions of several cytogenetic alterations associated with the pathogenesis of the tumor, such as the connection with Beckwith-Wiedemann Syndrome and familial adenomatous polyposis, for example (STEINMETZ L. et al., 2005). Histologically there are different subtypes: epithelial – fetal pattern, fetal and embryonic pattern, macrotrabecular, small undifferentiated cells; and mixed mesenchymal and epithelial cell types (DEVI, L. P et al., 2014).

It usually presents as progressive abdominal distension, palpable abdominal mass, abdominal pain and hepatomegaly (BRYONY L. et al., 2021). The only well-described tumor marker of hepatoblastoma is alpha-fetoprotein (AFP) - although not every tumor secretes this marker - predominantly produced in hepatocytes during pregnancy. At birth, the plasma concentration is high but progressively decreases until reaching normal levels between 8 and 24 months of age (PURCELL et al., 2012). Hepatoblastoma in patients with low levels of AFP is a clinical indicator of worse prognosis, not well understood etiologically, which classifies the tumor as high risk (DE et al., 2008).

Although most hepatoblastomas are associated with elevated AFP levels, there is another marker, human chorionic gonadrotophin beta (B-hCG), which is rarely described in the literature because it is a rare event, since only 18% of cases have a high level of B-hCG and, when present, generally high levels are associated with cases of precocious puberty (STEINMETZ L. et al., 2005).

Diagnosis of hepatoblastoma is based on images, with abdominal ultrasonography being the initial exam, AFP measurement, other laboratory tests (transaminases measurement, blood count, general exams), biopsy and tumor staging exams (Hiyama E., 2014).

The mainstay of treatment includes chemotherapy, surgical resection, and transplantation when necessary.

Chemotherapy starts soon after diagnosis and is also performed after liver transplantation (DEVI, L. P et al., 2014). Surgical resection plays an essential role in the management of hepatoblastoma and total resection is the only way to achieve cure. Surgical techniques and tools have advanced in recent decades, which greatly facilitated the accuracy of hepatectomies (TIANYOU Y et al., 2019).

CASE DESCRIPTIO

This report shows a pediatric patient aged 1 year and 4 months whose parents noticed an abdominal mass at the end of December 2021. On 01/20/2022 he was taken to the pediatrician, who confirmed the presence of an abdominal mass and requested an ultrasound (US) of the entire abdomen. The US showed an enlarged liver, at the expense of a large heterogeneous liver lesion, with echogenic foci forming a posterior acoustic shadow, measuring 13.3 cm in its largest diameter, with flow on the Doppler study, suggesting neoplasia. The patient was hospitalized for an abdominal tomography to be performed for further clarification, which showed a large heterogeneous liver mass affecting almost the entire right lobe, with lobulated contours, measuring 12.4 cm x 7.5 cm x 8.6 cm, with areas irregular hypoattenuating areas (necrosis? hemorrhage?) and foci of amorphous calcification in between. The pediatric surgeon on duty was contacted to perform a liver biopsy and the pediatric oncologist to follow up the case. The biopsy was then performed on 01/22/2022 and showed liver neoplasia with the appearance of a developing liver, compatible with Hepatoblastoma of mixed pattern (epithelial and mesenchymal); epithelial component showing cells with clear cytoplasm and small nuclei (fetal pattern) and cells with dense cytoplasm, enlarged nuclei and frequent mitotic figures (embryonic pattern); present vascular invasion. The material was also sent to the Bacchi laboratory, in Botucatu-SP, for immunohistochemistry.

On 27/01/2022, a contrast-enhanced magnetic resonance imaging of the abdomen was performed, which showed an enlarged liver at the expense of a voluminous expansive formation, containing intermingled areas of high signal on T1-weighted images, due to the hematic component, with frank restriction to diffusion and demonstrating enhanced heterogeneous by means of contrast, with intermingling intermingling septa, occupying almost the entirety of the right lobe and measuring approximately 12.6 x 10.0 x 7.4 cm; the lesion exerts a local mass effect, pushing the middle hepatic vein and gallbladder to the left, noting the medial lobulated component that is in contact with and contralaterally pushing back the pancreatic head; the right hepatic vein and the right portal branch are not identified, probably affected by the tumor, as well as the inferior vena cava. After the data from the exams, tumor staging was performed and the patient was classified as Mixed Pattern Hepatoblastoma – High Risk – PRETEXT II – V3+ (right hepatic vein and inferior vena cava) + P1 (right portal branch). The SIOPEL 4 high-risk protocol was then installed, with preoperative chemotherapy, definitive surgery to remove the tumor and postoperative chemotherapy.

In initial laboratory tests, performed on 28/01/2022, the following alterations were evidenced: B-hCG of 12 mLU/mL (reference value <1.06) and an AFP>300,000 ng/mL (reference value up to 8 .1 ng/ml). The patient was then referred for preoperative chemotherapy cycles and follow-up with laboratory tests. Serial controls of B-hCG and AFP were performed, with an increase in B-hCG up to 53 mLU/mL but with a subsequent decrease, and decreasing values of AFP. Three cycles of chemotherapy were

performed during the preoperative phase, followed by imaging tests after the end of each cycle. After the 3rd cycle, magnetic resonance imaging was performed, which showed a reduction in the index lesion, estimated at 75%, compared to 27/01/22, with no evidence of secondary abdominal injuries.

On 19/05/2022, the patient underwent liver tumor resection with a pattern already well differentiated from hepatoblastoma after neoadjuvant therapy, measuring 7 x 5 cm. In the surgical description, the tumor was restricted to the liver and the external surface of the hepatic capsule was free of neoplastic involvement with a circumferential surgical margin free of neoplasia (neoplasm 0.2 cm from the surgical margin).

After tumor resection the patient underwent postoperative chemotherapy in 3 courses every 3 weeks. During treatment B-hCG and AFP values fell to <0.1 mLU/mL and 6.3 ng/mL respectively. At the end of the treatment, the patient underwent a new magnetic resonance imaging of the abdomen for control, which showed signs of right hepatectomy, with enlargement of the left lobe, preserved morphology and signal intensity; spleen and pancreas with normal morphology, contours, dimensions and signal activity; surgical absence of the gallbladder, without signs of complications or secondary abdominal injuries. The patient then went into remission and will be followed up by the oncologist for a period of 10 years, with both laboratory and imaging tests.

DISCUSSION

Cancer is a disease caused by numerous factors at different levels of complexity. In a modern-day study of the genetics of cancer, Hanahan and Weinberg asserted that the basis of cancer lies in an accumulation of alterations that allow cells to evade the homeostatic control between proliferation and cell death (HANANAN and WEINBERG, 2011).

Childhood cancer encompasses a group of diseases that have in common the uncontrolled proliferation of aberrant cells and that can occur anywhere in the body. Because they are predominantly of embryonic origin, they are made up of undifferentiated cells, which, in most cases, provide a better response to treatments (INCA, 2022).

Hepatoblastoma is one of the most common tumors in childhood. As for histopathology, HBs are macroscopically well circumscribed and can be single or multiple. Microscopically, they are quite heterogeneous, with undifferentiated cells and immature epithelial cells (ROWLAND, 2002; SCHNATER et al., 2003). Hepatoblastomas are subdivided into epithelial (approximately 56% of cases) and mixed (epithelial and mesenchymal, which correspond to approximately 44% of cases) (SCHNATER et al., 2003).

Epithelial hepatoblastoma is divided into three: fetal, embryonic and small undifferentiated cells. Cells of the fetal subtype are well differentiated, with occasional mitoses. The embryonic subtype is poorly differentiated and the undifferentiated small cell subtype, also known as anaplastic, has tiny cells (ROWLAND, 2002; SCHNATER et al., 2003).

The relevance of histological subtypes as a prognostic factor is still under investigation. There are reports that tumors with a higher degree of cell differentiation, with a predominance of the fetal epithelial component, are usually less aggressive and have a better prognosis, while tumors of the subtype of small undifferentiated cells have an unfavorable prognosis (ROWLAND, 2002).

Serum levels of AFP provide measures of tumor burden and chemical sensitivity of the neoplasm. Longitudinal changes in AFP levels as well as changes in tumor volume or diameter are indicative of the possibility

of achieving tumor resection, which is universally recognized as a relevant factor in prognosis and chance of survival (Lovvorn HN et al., 2010) .

Although AFP is almost constantly detected in the serum of patients with hepatoblastoma, the unusual production of B-hCG by the liver tumor has already been confirmed both in vitro and in vivo, but the cellular origin of the production of this hormone has never been demonstrated (SHOJIROH M et al., 1983). Currently, studies have shown that the gradual decrease in the level of HCG after adequate treatment, suggest that the level of HCG may become another important biological marker of hepatoblastoma (ZHI T et al., 2021).

Clinically, hepatoblastoma appears similar to other liver tumors, with abdominal distention or a palpable abdominal mass, often associated with nonspecific symptoms such as the anorexia, pain, fatigue and weight loss (Sharma D et al., 2017). There are reported cases of fractures in approximately 15% of newly diagnosed children, most commonly in the ribs and spine. These children may also have irritability or bone pain (Towbin A.J et al., 2018).

The diagnosis is based on the dosage of AFP and beta-hCG, in addition to a complete blood count associated with liver enzymes, bilirubin and lactic dehydrogenase (LDL). In addition, imaging tests such as magnetic resonance imaging with gadolinium (a contrast that enhances neoplastic cells) and computed tomography of the chest and abdomen are part of the diagnosis. Abdominal ultrasonography can usually be used to verify the involvement of blood vessels. However, biopsy and immunohistochemistry are responsible for the final diagnosis (National Cancer Institute, 2022).

Regarding treatment, hepatoblastoma is extremely sensitive to chemotherapy (SHANMUGAM N et al., 2017). Although multidisciplinary treatments such as surgery, targeted therapy, interventional therapy and immunotherapy are gradually being developed, surgical resection combined with chemotherapy is still the main therapeutic option. Preoperative (neoadjuvant) chemotherapy can effectively decrease tumor size and provide the opportunity for total resection. On the other hand, postoperative consolidation chemotherapy can effectively prevent residual tumor recurrence and improve cure rates (MARIN JJG et al., 2019). Hepatoblastoma can spread throughout the body, most often to the lungs, but even when metastatic it has the potential to be cured with neoadjuvant chemotherapy (DEVI, L. P et al., 2014).

The prognosis of hepatoblastoma depends on some factors, such as the size of the tumor at diagnosis, the histology of the tumor (tumors with greater differentiation have a better prognosis), whether the tumor is metastatic, how the tumor responded to chemotherapy, whether the tumor could be removed completely with surgery, whether AFP levels have dropped after treatment, and whether the cancer has just been diagnosed or is relapsed (National Cancer Institute, 2022).

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