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RESEARCH ARTICLE

HEPATOCELLULAR CARCINOMA IN CHILDREN: 2 CASE REPORT

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Abstract

Background: Hepatocellular carcinoma (HCC) is the second most common liver cancer in children.In this article we sought, through our two observations, to examine the evolving clinical aspect as well as the therapeutic management of hepatocellular carcinoma in children, since this affection is rare in the childhood.

Case presentation: We report two cases of hepato carcinoma. The first case of an 11-year-old girl from Marrakech with glycogenosis complicated by hepatic cirrhosis at the portal hypertension stage. After diagnostic confirmation; the patient benefited from systemic treatment with Atezolimumab + Bevacizumab with good progress in the short term (5 months follow-up). The second case concerns a 14-year-old girl from Marrakech region with hepato carcinoma on a healthy liver who received the same treatment but the evolution was marked in the long term by an increase in the size of the mass and portal hypertension and death at age 17 years old.

Conclusion: HCC is rare in childhood. The etiological predisposition and biological behavior differ from adults. In cases of cirrhosis or liver disease, HCC must be suspected based on a high AFP level and an abnormal nodule on ultrasound. Hepatoblastoma should be considered first in the differential diagnosis. Treatment of pediatric HCC is difficult. Complete surgical resection is essential to cure it. For tumors that cannot be resected, liver transplantation is decided on a case-by-case basis. However , HCC remains difficult to treat as cure requires complete surgical resection.

Introduction:-

Hepatocellular carcinoma (HCC) is the second most common liver cancer in children, after hepatoblastoma. The majority of pediatric HCC patients do not have underlying liver disease and,therefore, they can generally tolerate pre- and post-operative chemotherapy. However, different strategies have been explored to convert unresectable HCCs into resectable tumors, such as systemic therapy and local-regional therapy.

Materials and Methods:-

Through our two observations we report the clinical, paraclinical, evolutionary aspect as well as the therapeutic management of the hepatocarcinoma, a fairly rare disease in the pediatric population.

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Comments:

Case 1:

ZA girl aged 11originated from Marrakech followed for glycogenosissince the age of 3, revealed by hepatomegaly and episodes of hypoglycemia confirmed on liver biopsy. The patient was placed on a diet rich in slow sugars for 3 years. At the age of 6, the patient's condition progressed to cirrhosis at the stage of portal hypertension. Faced with this picture, the patient was placed on vitamin therapy, strict monitoring of saturation, an esophago-gastro-duodenal fibroscopy every year to look for esophageal varices and an annual trans-thoracic echocardiography.

At the age of 11 the patient presented abdominal pain in the right hypochondrium isolated.Abdominal CT scan revealed chronic liver disease at the stage of portal hypertension; Site of a segment IV hepatic nodule.

In front of this table, an Alpha-feto protein assay was done, which was high at 8095 IU/ml, normal carcinoembryonic antigen at 1.9 ng/ml; The liver assessment showed a normal prothrombin level of 68% without hepatic cytolysis, the viral serologies carried out revealed negative.

Imaging by magnetic resonance revealed a nodular lesion of segment IV measuring 33*27 mm on the liver of chronic liver disease with signs of portal hypertension (figure 1).

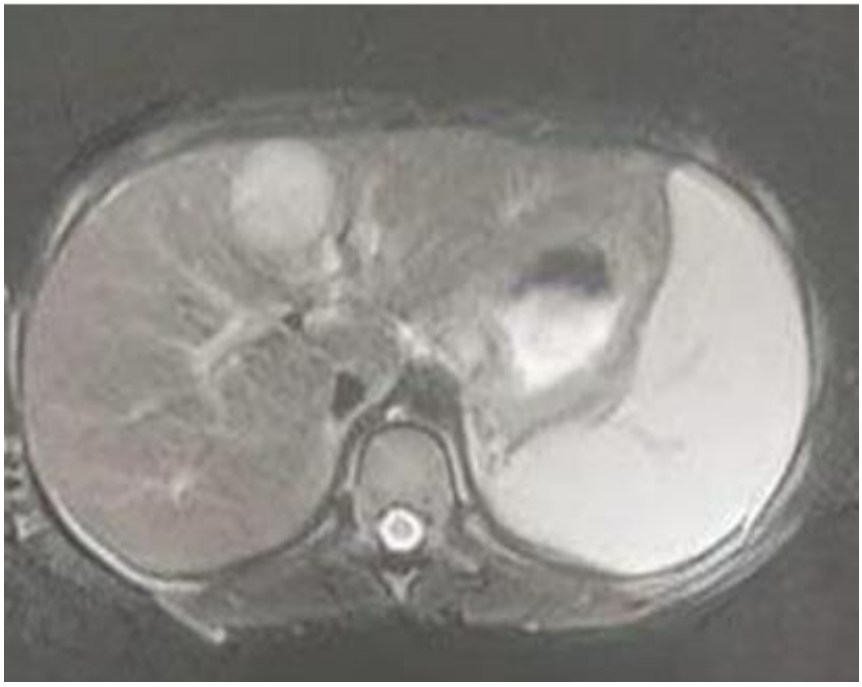

Figure 1:- Imaging by magnetic resonance imaging a nodular lesion of segment IV measuring 33*27 mm on the liver with chronic hepatopathy.

A diagnostic liver biopsy revealed hepatocellular carcinoma.

A partial hepatectomy was done with anatomical pathological study objectifying an aspect morphology of 30 mm hepatocarcinoma in cirrhosis with healthy boundaries.

As part of the extension assessment, a thoracoabdomino-pelvic CT scan was performed, revealing no secondary lesion.

The patient was placed on first-line treatment with bevacizumab at a dose of 7.5 mg/kg/3 weeks and Atezolizumab at a dose of 1200 mg/3 weeks.

The evolution was marked by thrombocytopenia due to portal hypertension, thus delaying treatment. The patient benefited from two cycles for 4 months. The follow-up is 5 months.

Case 2:
A 14-year-old girl from Marrakech region with no particular pathological history presented with an incidental discovery of a liver mass revealed by imaging following abdominal trauma complicated by extensive hemoperitoneum. The Alpha-feto protein assay was done and was normal at 1.6 ng/ml. The liver assessment showed a normal prothrombin level of 67% without hepatic cytolysis; the hepatitis C and B serologies were negative.

Abdominal CT scan revealed a large hepatic mass involving segments IV, V and VIII measuring 10.4*7 cm by 12 cm associated with a right lateral uterine mass probably of ovarian origin associated with subdiaphragmatic lymph nodes with infiltrated appearance of the mesenteric fat and peritoneal effusion of moderate abundance.

The anatomo-pathological study of liver biopsy revealed a fibrolamellar type hepatocellular carcinoma.

As part of the expansion assessment, the Thoraco-abdomino-pelvic tomography did not reveal any secondary lesions.

The patient was placed on sorafenib at a dose of 800 mg/day with assessment of skin and biological digestive tolerance for 1 year. The treatment was stopped due to unavailability then placed on Bevacizumab at a dose of 15 mg/kg/3 weeks and Atezolizumab at a dose of 1200 mg/3 weeks having received 12 cycles.

The evolution was marked by the regression of 25% of the liver mass after 5 months from the start of treatment then gradually increase in size to a size of 18 * 17 * 13 versus 10.4 * 7 * 12 with signs of compression and signs of portal hypertensionmade of splenomegaly 32*6.6cm. Faced with this picture, the patient received splenic radiotherapy. One week later, the patient died in hemorrhagic shock due to upper gastrointestinal bleeding.

Discussion:-

In childhood, primary liver tumors are rare. They represent approximately 1% of malignant solid organ tumors in children (1). Pediatric hepatocellular carcinoma is the second most common liver malignancy in children, after hepatoblastoma (2). The difference between the sexes is not as obvious as in adults, and white and black children have the same predisposition (3).

Two subgroups of HCC exist in childhood. The first subgroup includes HCC that develops against the background of cirrhosis or underlying liver diseases such as perinatal acquired diseases, hepatitis B virus infection, tyrosinemia, glycogenosis, Alagille syndrome, progressive familial intrahepatic cholestasis and congenital portosystemic shunts. The second subgroup includes HCC that develops without prior liver disease (1,3).

Clinical symptoms and signs of pediatric HCC include abdominal pain, abdominal mass, jaundice, cachexia, hepatosplenomegaly, and gastroesophageal reflux in advanced cases; and in the setting of chronic liver disease, there may be signs of portal hepatic hypertension and chronic liver failure. On palpation, the liver is often irregular, hard, and has a nodular surface (4).

Only 55 to 65% of children with HCC have an increase in serum Alpha-fetoprotein (5). Based on its histological characteristics, childhood HCC has been divided into three groups: conventional HCC, the second transitional type has characteristics of both HCC and hepatoblastoma, and the third is fibrolamellar HCC, which accounts for a quarter cases of pediatric HCC.

An elevated AFP level and an abnormal nodule on ultrasound suggest HCC in a child with cirrhosis or liver disease. Although serum AFP level is not very accurate, it has fairly good specificity for detecting HCC in at-risk patients (6).

Imaging methods can incidentally determine up to one third of pediatric HCC (7).

Ultrasound reveals a hyperechoic mass with variable sizes and hypervascularization (3). Further examination of the mass requires dynamic imaging studies such as computed tomography (CT) or magnetic resonance (MRI) using contrast material.

Although biopsy is not recommended in pediatric patients, Khanna et al. suggested histological evaluation in children without cirrhosis (8).
For the differential diagnosis, hepatoblastoma is in the first place. In patients under five years of age, low birth weight, maternal preeclampsia, smoking parents, having familial adenomatous polyposis and trisomy 18 suggest hepatoblastoma.AFP and imaging techniques may not be helpful in differentiating from HCC. The presence of calcification, necrosis, and cystic areas in the mass may indicate the existence of hepatoblastoma. Histopathologically, the presence of embryonic or mesenchymal epithelium suggests hepatoblastoma. Differentiation of HCC in older children should consider masses such as adenoma, focal nodular hyperplasia, and undifferentiated embryonal sarcoma (9).

Treatment of HCC in children is difficult. Curative treatment requires complete surgical resection. In 70% of cases, pediatric HCC occurs in a normal liver. Due to sufficient hepatic reserve, the absence of concomitant liver disease may allow a tolerable apparent anatomical resection.

However, less than 20% of patients in pediatric HCC are eligible for resection, while others are not eligible due to advanced stage (multifocal disease, vascular invasion) (1). For untreatable tumors, liver transplantation should be preferred. The 5-year survival rate of children with HCC has improved significantly over the past 40 years, from 4% to 10% to 56% to 80%. The development of strict monitoring and surgical methods is the main cause of this improvement (2).

In order to help make patients suitable for resection, various studies have used various combinations of chemotherapy to reduce tumor burden (9).

Historically, Patients with HCC were treated with the same protocol for hepatoblastoma(2). Evidence of chemo-response associated with surgical resection has led to the development of comprehensive protocols such as SIOPEL, which combines chemotherapy and surgical resection.

In the HB99 study conducted by the German Society for Pediatric Oncology and Hematology (GPOH) between 1999 and 2008, in children who underwent complete tumor resection and treated with 2 cycles of carboplatin (200 mg/m2/d × 4) and etoposide (100 mg/ m2/d × 4), overall survival over 3 years was 89% of cases. However, in children with inoperable or metastatic disease, the prognosis was poor with a survival of 20% (2).

In the particular case of waiting for liver transplantation for HCC with the impossibility of continuing intra-arterial treatments (thrombosis or dissection of the hepatic artery), numerous series report the use of tyrosine kinase inhibitors which do not seem to have caused harm to the surgical procedure or the medium- and long-term prognosis;The first pediatric series involving 12 children with advanced HCC treated with sorafenib have been published. Six of these 12 children who underwent liver resection (n = 4) and liver transplant (n = 2) received sorafenib/PLADO and after 20 months there were no recurrences. Three (43%) of 7 patients with tumor at diagnosis became resectable (10).

With the arrival of the atezolizumab + bevacizumab combination, the systemic treatment of hepatocellular carcinoma has changed significantly. This new therapy requires training in the toxicity of these treatments and in particular in immuno-mediated toxicities. Systemic treatments for HCC are reserved for the advanced stage of the disease in patients with Child A cirrhosis in good general condition (11), for patients presenting with HCC with vascular invasion, and/or extra-hepatic metastases or at the less advanced stage having resisted two consecutive sessions and intra-arterial loco-regional treatment.

For the case of our patients; systemic treatment was indicated in the first patient given the history of hepatic cirrhosis, on the other hand the second patient treatment was indicated given the lack of improvement under sorafenib.

There are limited data on radiological interventions including transarterial embolization, radio frequency ablation, transarterial radio embolization, transarterial chemo embolization, and hepatic arterial infusion chemotherapy in children with HCC(12).

Liver transplantation has been suggested as the most radical and curative treatment for pediatric HCC without extrahepatic malignancy(1,2).
All children with underlying liver disease, hereditary or acquired, should be monitored with AFP and ultrasound at 6-month intervals. In children with PFIC type 2 and tyrosinemia, the follow-up interval should be reduced to 3 months, and in inactive HBV carriers it can be extended up to 1 year (4).

Conclusion:-

A rare tumor in pediatrics, HCC remains difficult to treat as cure requires complete surgical resection. For this reason, several neoadjuvant chemotherapy protocols have been developed. For tumors that cannot be treated, systemic treatment and liver transplantation remain the most effective treatments and should be chosen on a case-by-case basis.

Declarations

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Ethical Approval
As this is a case series which do not containany patient identification details, ethical approval is not required.

Informed Consent
Writtenin formed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal."

Author Contribution
The author confirms sole responsibility for study conception and design, data collection, analysis and interpretation of results, and manuscript preparation

Conflicts of Interest
The authors declare no conflicts of interest.

Availability of supporting data
The data and documents used in the completion of thiswork are stored in the variousarchivalfacilities of the Mohamed the VI universityhospitl of Marrakech. Their consultation is possible subject to legalcoverageaccording to the laws in force in Morocco.

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