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LIVER CANCER ASSOCIATED WITH HEPATITIS B VIRUS INFECTION IN A CHILD: A CASE REPORT

KANKER HATI YANG BERKAITAN DENGAN INFEKSI VIRUS HEPATITIS B PADA ANAK : LAPORAN KASUS

Karina Pharamita Dewi, Rendi Aji Prihaningtyas, Bagus Setyoboedi *, Sjamsul Arief

Department of Child Health, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
Department of Child Health, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Case Study
Studi Kasus

A B S T R A C T

Background: *Two-thirds of primary liver tumors in children are malignant. Hepatoblastoma (HBL) accounts for 40-60 percent of pediatric liver tumors and is the most common malignant liver tumor. Hepatocellular Carcinoma (HCC) is the second most common malignancy in children, accounting for approximately 20% of cases. Both malignant liver tumors have similar clinical and imaging features, but different prognosis and treatment.* ***Purpose:*** *This report aims a case of liver cancer related to hepatitis B virus infection in a child.* ***Case analysis:*** *A 15-year-old girl presented with a two-month history of right upper quadrant pain along with abdominal distension, weight loss, back pain, anorexia, nausea, weakness and fatigue for 5 months prior to admission. Physical examination revealed a hard, firm mass with a bumpy surface in the right upper quadrant of the abdomen and splenomegaly. Laboratory test showed an increase in Lactate Dehydrogenase (LDH), Gamma-Glutamyl Transpeptidase (GGT), Alpha Feto Protein (AFP), quantitative Hepatitis B Virus (HBV) DNA, and HBsAg reactive. Abdominal Multi-Slice Computed Tomography (MSCT) revealed malignant solid mass with necrotic component inside, indistinct borders, irregular margins and kissing spleen.* ***Result:*** *The diagnosis of liver cancer in this patient suggested HCC associated with chronic hepatitis B infection.* ***Conclusion:*** *Routine follow-up of all children with chronic hepatitis B infection is crucial because of the risk of developing liver cancer in adolescence and adulthood.*

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Correspondence:
Bagus Setyobudi

E-mail :
bagus.setyoboedi@fk.unair.ac.id

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A B S T R A K

Latar belakang: Dua pertiga tumor hati primer pada anak bersifat ganas. Hepatoblastoma (HBL) menyumbang 40 - 60% tumor hati pada anak-anak, yang merupakan tumor hati ganas paling umum pada anak. Karsinoma Hepatoseluler (HCC) menyumbang sekitar 20%, yang merupakan tumor hati ganas kedua yang paling umum pada anak. Kedua tumor hati ganas ini memiliki beberapa gambaran klinis dan pencitraan yang mirip namun prognosis dan pengobatannya sangat berbeda. **Tujuan:** Laporan kasus ini bertujuan untuk mendeskripsikan penyakit kanker hati yang berhubungan dengan infeksi virus hepatitis B pada anak. **Analisis kasus:** Seorang anak perempuan berusia 15 tahun datang dengan keluhan nyeri kuadran kanan atas selama dua bulan sebelum masuk rumah sakit, disertai gejala lain, termasuk distensi perut, penurunan berat badan, nyeri pinggang, anoreksia, mual, lemas, dan kelelahan sejak 5 bulan sebelum masuk rumah sakit. Pada pemeriksaan fisik didapatkan massa padat keras dengan permukaan tidak rata di kuadran kanan atas dan splenomegali. Terjadi peningkatan kadar *Lactate Dehydrogenase* (LDH), *Gamma-Glutamyl Transpeptidase* (GGT), *Alpha Feto Protein* (AFP), Hepatitis B Virus (HBV) DNA kuantitatif, dan HBsAg reaktif pada pemeriksaan laboratorium. *Multi-Slice Computed Tomography (*MSCT) abdomen menunjukkan massa padat ganas dengan komponen nekrotik di dalamnya, batas tidak jelas, tepi tidak beraturan, dan kissing spleen. **Hasil:** Diagnosis kanker hati pada pasien ini lebih mengarah pada karsinoma hepatoseluler yang disertai infeksi hepatitis B kronis. **Kesimpulan:** Tindak lanjut rutin perlu dilakukan pada semua anak dengan infeksi B kronis karena risiko terkena kanker hati pada usia lebih tua.

Kata kunci:
Anak, Hepatitis B, Hepatoblastoma, Karsinoma hepatoselluler, Kanker hati

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INTRODUCTION

Pediatric liver cancer often develops in otherwise healthy livers and generally carries a poor prognosis. This liver cancer may be associated with congenital abnormalities, genetic syndromes or metabolic conditions. Hepatoblastoma (HBL) and Hepatocellular Carcinoma (HCC) are two major neoplasms accounting for 0.5 - 1.5% of all pediatric neoplasms. These two neoplasms also account for 4% of all Orthotopic Liver Transplants (OLT) in children. Hepatoblastoma accounts for 67-80% of all childhood liver cancers worldwide, while HCC accounts for 20-33%. The incidence of HCC depends on geographic and demographic factors and is related to the incidence of hepatitis B in the population (Khanna and Verma, 2018). Childhood HCC has a poor prognosis, with less than 30% disease-free survival compared to HBL, which has over 80% disease-free survival (Digiacomo *et al*., 2023).

Hepatocellular Carcinoma (HCC) is the second most common primary liver malignancy in childern after HBL, accounting for approximately 27% of cases. The remaining pediatric promary liver malignancy cases are vascular tumors and sarcomas. Overall primary liver malignancies are extremely rare, accounting for only 1% of all pediatric malignancies, with less than 1.5 cases per million in children under age of 18. Hepatoblastoma accounts for more than two-thirds of these cases, with HCC and the very rare embryonal sarcoma of the liver accounting for the other cases. Hepatocellular Carcinoma occurs mostly in older children and adolescents, either in a noncirrhotic liver or associated with various fibrosing diseases or cirrhosis of varying etiology (Ranganathan *et al*., 2020).

A total of 257 - 291 million people worldwide are chronically infected with Hepatitis B Virus (HBV), but may remain asymptomatic for many years. However, they can potentially transmit the infection to others by perinatal, percutaneous, and sexual exposure or by close person-to-person contact. Complications such as cirrhosis, liver failure, and HCC, which are the leading causes of HBV-related death, are estimated to occur in 15 - 40% of HBV-infected patients (Lim *et al*., 2020; Tajiri *et al*., 2016) World Health Organization (WHO) has committed to eliminating HBV, but this is difficult to achieve due to social barriers, including stigma, embarrassment, denial, isolation, and depression, that cause chronic HBV patients to conceal their infection and not seek treatment (Roma *et al*., 2024). This report aims to discuss a case of liver cancer associated with hepatitis B virus infection in a child. Serious complications from hepatitis B in children are well established, therefore early prevention of hepatitis B should be implemented.

CASE STUDY

A 15-year-old girl presented to the Pediatric Outpatient Clinic with Right Upper Quadrant (RUQ) pain for 2 months and other symptoms, including abdominal distention, back pain, weight loss, anorexia, nausea, general weakness, and fatigue for 5 months prior to admission. Data revealed that the patient's maternal grandmother had died several years ago from liver cancer, and the patient's biological mother had also suffered from HBV infection, with seropositive results on HBsAg blood examination. Previously, the patient had been taken to the local regional hospital, where a serological examination also revealed positive serology HBsAg results. The family has been advised to seek further management. However, due to the pandemic, the patient's family postponed the follow-up. The patient's physical examination showed abdominal distension, splenomegaly without venous dilatation. In the right upper quadrant of the abdomen, a hard, solid mass with an irregular surface pas palpable.

RESULT

The complete blood count revealed anemia (Hb 7.6 g/dL, Hct 22.6%, leucocyte $8.81x10^3$/µL, thrombocyte $526x10^3$/µL). Liver function tests showed elevated Aspartate Aminotransferase (AST) 348 U/L, normal Alanine Aminotransferase (ALT) 29 U/L, elevated Lactate Dehydrogenase (LDH) 252 U/L, HBsAg reactive >1.000, Alkaline phosphatase (ALP) 171 U/L, Gamma-Glutamyl Transpeptidase (GGT) 215 U/L, Alpha Feto Protein (AFP) >1.000 IU/ml, and HBV DNA 364 copies/ml (Log 2.56). Abdominal ultrasound showed a normal-sized liver with a hypoechoic lesion measuring 6.2 x 5.2 x 7.1 cm in segments 5 - 6 of the right lobe, vascularization within the lesion (+), and suspicion of a right lobe hepatoma in segment 5 - 6 can be seen in Figure 1. After admission, chest x-ray was performed due to shortness of breath. Rough nodules were seen on both lungs, suggesting metastatic process to the lungs can be seen in Figure 2.

A real-time Multi-Slice Computed Tomography (MSCT) scan of the abdomen revealed a liver enlargement with a mean craniocaudal length of approximately 25.56 cm, resulting in a kissing spleen. A solid mass (38 - 41 HU) with a necrotic component in the interior (25 HU), ill-defined margins, irregular borders ± 13.7 x 17.2 x 25.56 cm was identified in the right lobe. In segment II of the left lobe, the largest size of approximately 2.2 x 2.1 x 3.5 cm showed contrast enhancement (93 HU). The lesion seemed

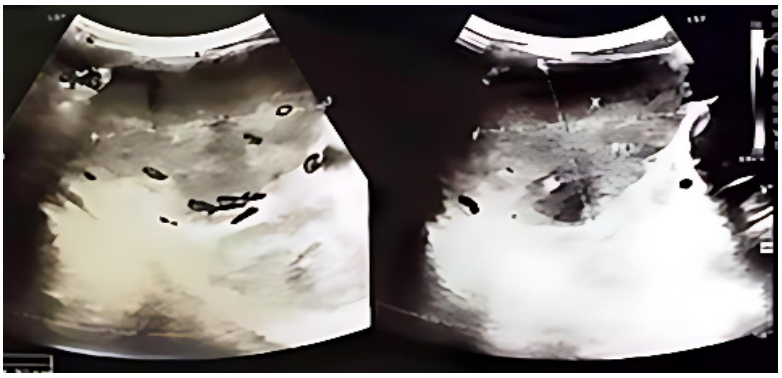

Figure 1. Abdominal ultrasonography showed hypoechoic lesion

Figure 2. Chest radiograph showed rough nodules on both lungs

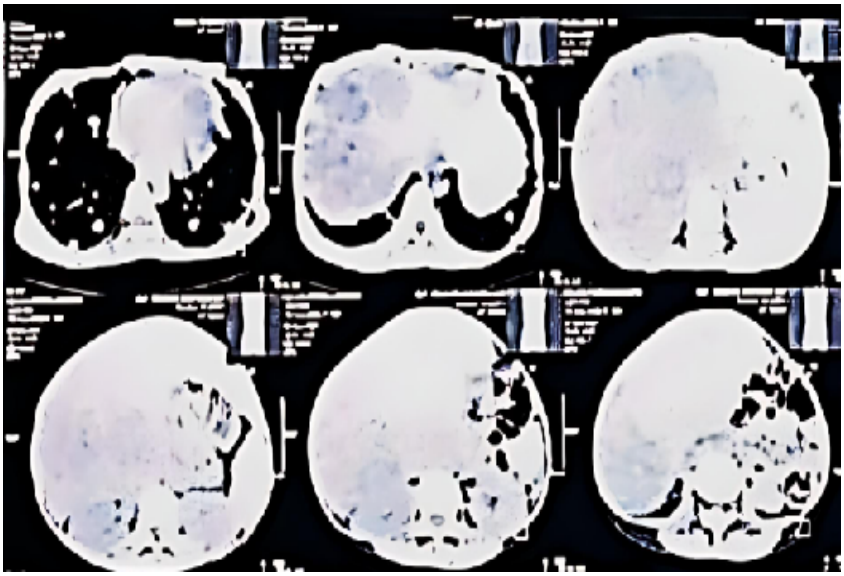

Figure 3. Multi Slice Computed Tomography (MSCT) scan of the abdomen revealed a liver enlargement with solid mass

to be nourished by the right and left hepatic artery. Additionally, a mass was found pressing the right kidney posteriorly, no thrombus or AV fistula was observed (Figure 3). Based on the patient's history, physical examination, laboratory findings and radiological results, HCC was suspected. Liver biopsy was not performed due to the clinical condition. Supportive care was initiated with packed red blood cell transfusion and oxygen supplementation.

DISCUSSION

Liver tumors account for approximately 1% of all neoplasms in children, with an annual incidence of about 1.4 per million in children under 16 years of age. Hepatocellular carcinoma is the third most common type of liver tumor, accounting for 65% of cases in children under 10 years of age. It is more common in boys than girls (Yantie *et al*., 2016). Chronic HBV infection,

hepatitis C virus infection, and alcohol abuse are major contributing factors (Pinto *et al*., 2024). The hepatitis B virus belongs to the Hepadnaviridae family and similar to retroviruses, possessing a typical characteristics. HBV is classified into different genotypes that have specific geographic distributions and subgroups (Camara *et al*., 2023).

There are several routes of transmission of HBV, including parenteral (such as through transfusions, reused needles and syringes and blood contact), vertical, sexual, and horizontal (such as through contact with bodily fluids, such as saliva, shared toothbrushes, and skin lesions) (Lee, 1997). In high endemic countries (Africa and Southeast Asia), HBV infection is acquired predominantly during the perinatal period or in early childhood (Borgia *et al*., 2012). Chronic HBV infection affects 70 - 90% of infants born to HBeAg positive mothers in the absence of active and passive immunization (Zou *et al*., 2012). According to the National Basic Health Research (RISKEDAS), Hepatitis B Surface Antigen (HBsAg) is found in 7.1% of the population, or around 18 million Indonesians. While universal infant hepatitis B immunization programs have reduced HBV infection rates, infection still persists among young children, as evidenced by a 4.2% prevalence of HBsAg among children under five years of age. The risk of HBV infection can be reduced by administering the hepatitis B vaccine along with Hepatitis B Immune Globulin (HBIG) within the first 12 hours after birth. In addition, antiviral therapy for the mother before the delivery is also recommended. Even though, the immunoprophylaxis of some cases cannot provide 100% protection; in fact, between 8-30% of infants can become infected (Yin *et al*., 2013). The high risk of vertical transmission may be due to failure in immunoprophylaxis which is often associated with HBeAg positivity and high maternal viral load (Filippo Villa and Navas, 2023).

HBV is primarily transmitted vertically from mother to child and horizontally in early childhood, causing chronic infection in adulthood (Indolfi *et al*., 2019). Chronic viral hepatitis causes hepatocytes to die and regenerate, which can lead to cancer (Yeh *et al*., 2023). Untreated chronic HBV infection can lead to cirrhosis of the liver and HCC, which is responsible for 96% of all deaths associated with hepatitis virus infection (Morais *et al*., 2023). The incidence of HBV-related HCC in childhood is low, but the prognosis is poor. At present, the mechanism of HBV-induced malignant transformation remains uncertain, and there are often inconsistent clinical manifestations or laboratory results for children with HBV-associated HCC among different studies (Mogul *et al*., 2018).

Patients with HCC remain asymptomatic for long periods. Generally, HCC is caused by complex interactions between genetic and environmental factors. The incidence is increasing in the HBV-infected population. There is an 80% association between HCC and chronic HBV infection in adults, and this condition can originate in childhood (Lim *et al*., 2020).

The signs and symptoms of HCC are very similar to those of HBL, but children with HCC are clinically worse than those of HBL. On the physical examination, there is an enlarged mass in the abdomen which is characterized by the presence of a lumpy mass in the liver. Radiologic findings are usually multifocal, variable, involving both hepatic lobes and may confuse the diagnosis (Alemayehu and Hailu, 2019; Murawski *et al*., 2016). Ultrasound screening can be used to detect up to 70% of HCC at an early stage so that further treatment can be carried out (Brusset *et al*., 2024). Although screening can be done by ultrasound, one of the limitations of ultrasound is that results depend on operator experience (Du *et al*., 2023). In our cases, multiple lesions were observed in both hepatic lobes, as diffuse HBL or metastases. Hepatoblastoma must be suspected when lesions are large and solitary (Yang *et al*., 2012).

Up to 50% to 60% of pediatric primary liver cancers in children are malignant. Hepatoblastoma accounts more than 60% of all pediatric liver malignancies, while 20% of all pediatric primary liver cancers are HCC. Hepatoblastomas originate from pluripotent hepatic stem cells that retain the ability to differentiate into hepatocytes and cholangiocytes. Treatment options include chemotherapy and surgical removal or, as a last alternative, liver transplantation. It appears that children with HBL have a better survival rate compared to children with HCC. Recently, about 75% of children with HBL can be completely cured (Zhuang *et al*., 2011). Hepatocellular Carcinoma surgery in children can be carried out partially (hepatectomy) or transplantation (Ziogas *et al*., 2020). The majority (70 - 90%) of patients with HCC associated with HBV infection have pre-existing cirrhosis, indicating the need for HBV therapy to preserve liver function and reduce HCC progression (Roberts *et al*., 2021).

However, the radiographic characteristics of these two conditions are quite different. Liquefaction may be caused by an intralesional necrosis or by a hemorrhage. Liquefaction is typically seen on ultrasound as a hypoechoic area in the center of the lesion. Calcifications occur in HBL, HCC, teratomas, and hemangiomas. Calcifications are not diagnostic specific. Liver biopsy may be used to determine the stage and other liver diseases (Hu *et al*., 2022). A biopsy is performed as the gold standard or when tissue cannot be resected and is necessary to guide nonsurgical therapy. Biopsy is performed based on each patient's condition because the risks of biopsy include tumor spread, bleeding, or other complications (Alshareefy *et al*., 2023).

Histologically, the calcifications were frequently associated with the mixed type of HCC, presumably due to the formation of osteosarcomatous foci. Calcification is rarely found in cases of HCC, which is associated with radiation therapy. Histologically, HBL appears as

a solitary, large, solid mass that may contain fibrous bands, resulting in a "spoked-wheel appearance". Typical fibrous septa are visible as gray areas in the ultrasound image (Zhao *et al*., 2021). In addition, liquid biopsies are a way of overcoming tumor heterogeneity, especially for multifocal and advanced HCC (Felden *et al*., 2017) but in this case, there is a metastatic process to the lung.

CONCLUSION

Chronic HBV infection in children is associated with the risk of liver cirrhosis and HCC. Our country has taken preventive measures through a national immunization program with quite good coverage rates. However, in cases of hepatitis virus infection acquired intrauterine that is via transplacental transmission from mothers to their babies, the most important step is to strengthen monitoring after detection by ensuring that every child born to a mother with Hepatitis B receives regular follow-up care and is closely monitored by a pediatrician by providing good education to patients and their families, regional health workers and the community, it is hoped that the incidence of transformation of HBV infection into liver malignancy in children can be reduced.

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