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Case Report

Successful liver transplant in a 15-year-old boy with hepatocellular carcinoma, portal vein thrombosis, paraneoplastic hyperlipidaemia and hypertension-induced PRES – a very rare case report

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Introduction

The liver is one of the most common metastatic sites for malignancy. Therefore, metastatic liver malignancies are more common than primary liver malignancies [1]. Hepatocellular carcinoma (HCC) is a primary malignancy of the liver which accounts for more than 90% of cases [2]. The incidence of HCC increases with age, with a peak at the age of 70 years [3]. Chronic hepatitis B, hepatitis C, alcoholic liver disease and nonalcoholic fatty liver disease are the most common risk factors for the development of HCC [4]. HCC in a young patient without risk factors is a rare occurrence [5]. HCC often exhibits paraneoplastic manifestations. Among them, hypercholesterolaemia, hypoglycaemia, hypercalcaemia, and erythrocytosis are common [6]. Hypertension is a rare paraneoplastic manifestation [7]. Vascular invasion, including portal vein tumor thrombosis (PVTT), is generally considered an absolute contraindication for liver transplant [8]. However, recent evidence shows significant long-term survival benefits from liver transplant in patients with HCC and PVTT after successfully down staging of the tumor burden [9].

We present an unusual case of HCC with PVTT and associated paraneoplastic hyperlipidaemia and hypertension in a young boy who underwent successful liver transplantation after downstaging of the tumor with chemotherapy.

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Case presentation

A previously healthy, 15-year-old boy presented with a one-week history of headache, regurgitation, vomiting and abdominal fullness. The headache, initially diffuse and moderate, became severe in the last two days before admission. He had no fever, meningism or signs of increased intracranial pressure. He reported reduced appetite and a 3 kg weight loss over the past month. There was no family history of chronic illnesses or malignancies, and he did not smoke or consume alcohol. After admission, he experienced three episodes of generalized tonic-clonic seizures, each lasting less than a minute and resolving spontaneously. The general examination was unremarkable, with a blood pressure of 170/100 mmHg in both arms. Abdominal examination revealed a massive, non-tender hepatomegaly, without splenomegaly or ascites. There were no focal neurological signs including a normal fundoscopy.

On initial evaluation. his full blood count revealed normocytic normochromic anaemia and mild leukocytosis with a normal platelet count. His liver biochemistry revealed transaminitis with a markedly elevated alkaline phosphatase and gamma glutamyl transferase with marginally elevated bilirubin. His viral hepatitis panel was negative, and serum ferritin was normal (Table 1).

Table 1: Investigations

Investigations	Reference range	Values on admission	Values after completion of chemotherapy
WBC	4000 – 10,000/μL	11,300/μL	-
Neutrophil	50% - 70%	68.9%	-
Lymphocyte	20% - 40%	20.8%	-
Hemoglobin	13.2 – 16.5g/dl	10.4g/dl	-
MCV	80.0 – 100.0fL	80.6fL	-
Platelet	150,000 – 400,000/μL	340,000/μL	-
ESR	<20mm/1st hour	06mm/1st hour	-
CRP	0 – 5mg/L	05mg/L	-
Creatinine	70 – 115μmol/L	66.3μmol/L	-
Urea	8 – 50mg/dl	20.8mg/dl	-
Sodium	137 – 147mmol/L	135mmol/L	-
Potassium	3.5 – 5.1mmol/L	3.8mmol/L	-
Calcium	2.15 – 2.57mmol/L	2.3mmol/L	-
Magnesium	0.7 – 1.1mmol/L	0.7mmol/L	-
AST	0 – 35U/L	280U/L	44U/L
ALT	0 – 40U/L	70U/L	54U/L
ALP	46 – 116U/L	329U/L	102U/L
GGT	0 – 50U/L	508U/L	91U/L
Protein	6.0 – 8.5g/dl	7.4g/dl	6.6g/dl
Albumin	3.5 – 5.3g/dl	4.5g/dl	4.4g/dl
Globulin	2.5 – 3.5g/dl	2.9g/dl	2.2g/dl
Total bilirubin	5 – 19μmmol/L	23.8 μmmol/L	12.3μmmol/L
Direct bilirubin	0 – 5μmmol/L	6.6 μmmol/L	6μmmol/L
Indirect bilirubin		17.2 μmmol/L	6.3μmmol/L
INR	<1	0.82	-
Ferritin	18 – 464	151ng/ml	-
Total cholesterol	<240mg/dl	522mg/dl	126mg/dl
Triglyceride	<200mg/dl	175mg/dl	66mg/dl
HDL cholesterol	>60mg/dl	43mg/dl	44mg/dl

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LDL cholesterol	<160mg/dl	444mg/dl	69mg/dl
Alpha-fetoprotein	0 – 20ng/ml	>5000ng/ml	793.6ng/ml
CEA	0 – 2.5ng/ml	2.02ng/ml	-

WBC – white blood cells, MCV – mean corpuscular volume, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, AST – aspartate aminotransferase, ALT – alanine aminotransferase, ALP – alkaline phosphatase, GGT – gamma-glutamyl transferase, INR – international normalization ratio, CEA – carcinoembryonic antigen, VLDL – very low-density lipoprotein, EEG – electroencephalogram

An abdominal ultrasound scan (USS) revealed hepatomegaly with multiple focal liver lesions and mild splenomegaly. Contrast-enhanced computed tomography (CECT) of the chest, abdomen, and pelvis showed hepatomegaly with multiple hypo dense focal liver lesions in both lobes, a thrombus in the main portal vein, splenomegaly and mild ascites, without other organ involvement (Figure 1). Liver biopsy histology and immunohistochemistry confirmed malignant HCC (Figure 2). MRI of the brain showed T2/FLAIR hyper intense areas in the right occiput, indicating posterior reversible encephalopathy syndrome (PRES) (Figure 3).

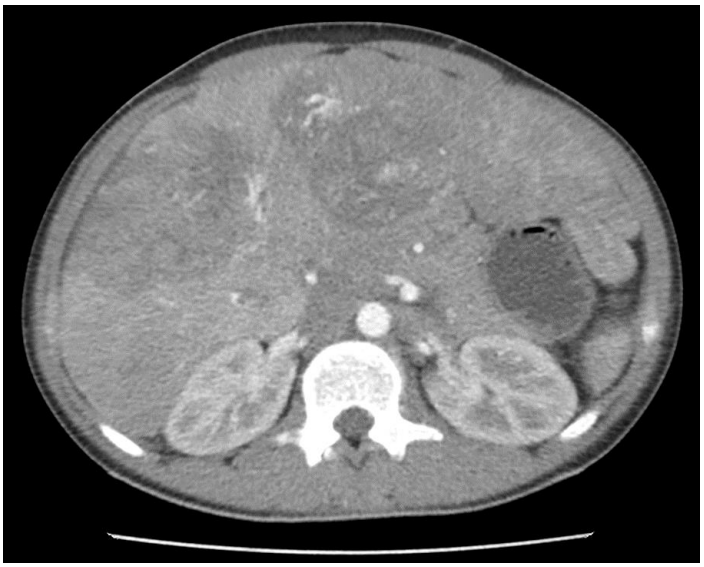

Figure 1: Initial CECT of abdomen showing multiple varying sized hypodense focal hepatic lesions in both lobe

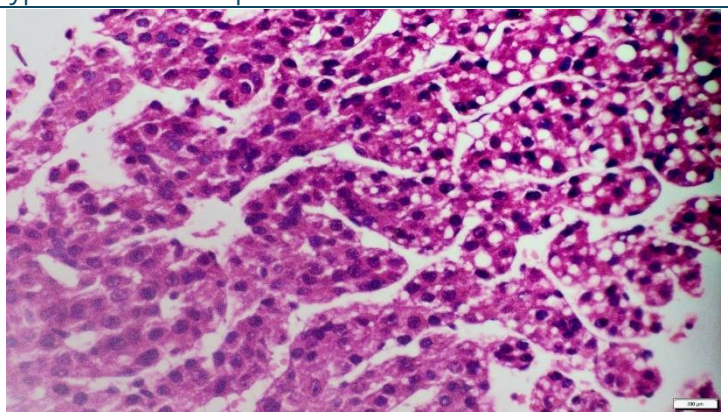

Figure 2: Liver biopsy revealed pleomorphic nuclei with prominent nuclei and abundant eosinophilic granular cytoplasm with indistinct cell borders with sparse mitosis

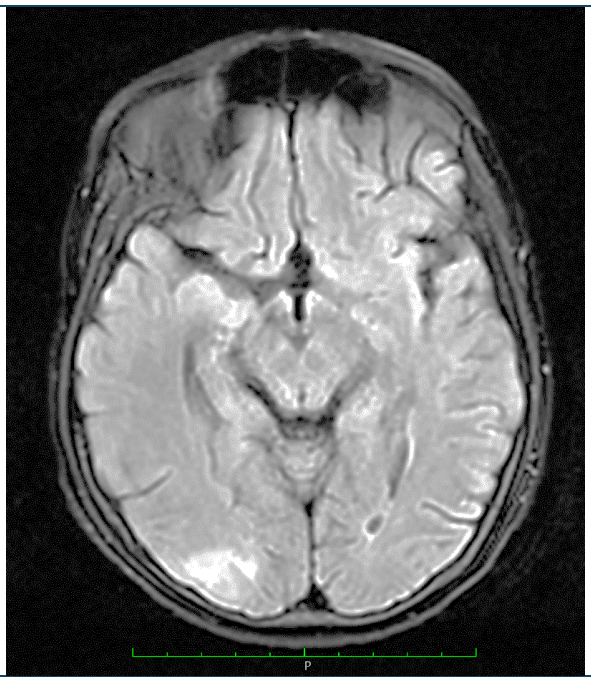

Figure 3: T2/FLAIR image of MRI brain showing high signal intensities in right occipital region

Serum alpha-fetoprotein was very high. His lipid profile revealed a high serum total cholesterol and very high low-density lipoprotein (LDL) cholesterol levels (Table 1). Plasma renin and angiotensinogen levels were not measured due to resource limitations.

Initially, blood pressure was managed with IV labetalol, followed by enalapril. Dyslipidaemia was controlled with rosuvastatin. Rivaroxaban was started for portal vein thrombosis following a normal upper gastrointestinal endoscopy (UGIE) that showed no varices. After discussions with a multidisciplinary team including gastroenterology, oncology and hematology, a collective decision was made to initiate neoadjuvant chemotherapy to downstage the tumor before liver transplantation.

The patient was started on cisplatin, doxorubicin and capecitabine-based chemotherapy and completed 5 cycles. CECT chest, abdomen and pelvis was repeated, which revealed significant improvement. A whole-body positron emission tomography (PET) scan was carried out and revealed multifocal hepatoma in both lobes which were non-fluorodeoxyglucose (FDG) avid with no metabolically active metastatic disease. Finally, he underwent a cadaveric whole liver transplantation. He had an uneventful recovery and is doing well with normal blood pressure and lipid levels without any targeted treatment.

Discussion

HCC is the common type of primary liver malignancy and accounts for more than 90% of cases. Malignancy of the liver and intrahepatic bile ducts is the sixth most common malignancy worldwide and is the third most common cause of cancer related mortality [8]. The incidence of HCC increases with advancing age, with the peak at 70 years. It is more prevalent in males [3].

Right upper abdominal pain, right hypochondrial swelling, and weight loss are the most common presentations of HCC [11]. Patients with HCC may occasionally develop paraneoplastic manifestations, and among them hyperlipidaemia is the most common. Genetic mutations in the LDL receptor gene in tumor cells lead to an abnormal receptor that lacks LDL binding capacity. Usually, LDL binding to receptor acts as negative feedback on HMG Co-A, the rate-limiting enzyme in cholesterol biosynthesis. Due to the above defective mechanism LDL production is also increased [12]. It is also postulated that proprotein-convertase-subtilisin-kexin type-9 (PCSK9) secreted by tumor cells plays a role in hyperlipidaemia [13]. Paraneoplastic hypertension is very rare in HCC and is due to an excessive secretion of either renin, angiotensinogen or angiotensin by the malignant cells [7].

PRES is a neurological disorder diagnosed on clinical and radiological findings. This is usually characterized by headaches, altered consciousness, visual disturbances and seizures. It can occur in various conditions. Among them, hypertension is common. The diagnosis is usually based on the clinical and MRI features which demonstrate prominent cortical and subcortical white matter signal hyperintensity on T2 flair involving bilateral occipital lobes specially in diffusion-weighted images. This condition is usually but not always reversible with appropriate management [12]. Our patient development recurrent seizures due to PRES caused by hypertension.

Diagnosis of HCC is based on non-invasive criteria and/or histopathological assessment. But non-invasive criteria can only be applied to cirrhotic patients. In non-cirrhotic patients, the diagnosis should be confirmed by histopathological assessment as in this case [8]. Imaging techniques, such as contrast 4-phase CT or dynamic contrast MRI should be used first due to higher sensitivity. Diagnostic hallmark in imaging is a combination of hypervascularity in the late arterial phase and washout in the portal venous phase [8]. Histopathological diagnosis of HCC is by the International Consensus Group for Hepatocellular Neoplasia criteria based on cytological and histological atypia with interstitial and vascular invasion. The histopathological diagnosis should be supplemented by immunohistopathological markers linked to malignant transformation of hepatocytes. The most common antibodies for HCC are Glypican-3 (GPC3), heat shock protein 70 (HSP70) and glutamine synthetase (GS) [15]. Hep par 1 is also a reliable immunohistochemical marker in HCC [16]. Hep par 1 was positive in our patient.

Surgical resection is recommended as the treatment of choice in patients with HCC arising from a non-cirrhotic liver [8]. Liver resection is recommended for single HCC of any size. Milan criteria are used for surgical resection as well as liver transplantation (LT) which are a single tumor ≤ 5cm or multiple tumors ≤ 3 nodules ≤ 3cm in size, without vascular invasion. But when nodular size is more than 2cm or two to three nodules within Milan criteria may be eligible for liver resection, if hepatic function is preserved, and sufficient liver volume be maintained [8]. LT is the first line option for HCC within Milan criteria but unsuitable for resection. Tumor vascular invasion and extrahepatic metastases are absolute contraindications for LT [8]. However, a recent meta-analysis of 14 studies revealed that patients with HCC and portal vein invasion can undergo LT after

successful downstaging of tumor [9]. Our patient also underwent LT after successful downstaging of cancer with chemotherapy.

Sorafenib and lenvatinib are the standard first line chemotherapy and regorafenib is recommended as the second line [8]. Systemic doxorubicin has a response rate of more than 10% when used alone. But a combination of cisplatin, doxorubicin, and capecitabine was well tolerated by patients, with a response rate of 24% in a study [17]. Our patient was started on cisplatin, doxorubicin, and capecitabine based chemotherapy and completed 5 cycles with a good response.

Conclusion

Although HCC is the most common primary liver malignancy, it is rare in young populations, with up to 10% of patients having no identifiable risk factors. Among its paraneoplastic manifestations, hyperlipidaemia is the most common, therefore it is reasonable to check lipid profile in a patient with HCC. Rarely paraneoplastic hypertension can develop. Therefore, it is reasonable to monitor blood pressure. Remarkably, liver transplantation can still be successful even in patients with vascular invasion, provided there is successful down staging of the cancer with neo adjuvant chemotherapy.

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