Case Report

Hereditary tyrosinemia presenting as hepatocellular carcinoma in a young infant

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ABSTRACT

Hereditary tyrosinemia type 1 is an inborn error of metabolism that affects numerous organs, particularly liver, kidneys and peripheral nerves. It usually presents in infants less than six months of age with features of liver failure, hepatoblastoma or hepatocellular carcinoma. Diagnosis is by a combination of clinical, biochemical and imaging features. We report here the case of a four months old infant presenting with massive hepatosplenomegaly and coagulopathy. He was detected to have hepatocellular carcinoma secondary to tyrosinemia and initiated on treatment. This report highlights the importance of considering tyrosinemia in the differential diagnosis of infants presenting with hepatic disease. Early diagnosis is important due to the presence of effective treatment and for prenatal diagnosis in subsequent pregnancies.

Keywords: Tyrosinemia, Infant, Hepatocellular carcinoma

INTRODUCTION

Tyrosinemia type I, also called as hepatorenal tyrosinemia is an autosomal recessive disease caused by defect in the enzyme involved in the degradation of tyrosine. This deficiency leads to an accumulation of substances that cause cellular damage. Clinical symptoms usually begin before 2 years of age. The majority of children present before the age of 6 months with evidence of acute liver failure and renal dysfunction. Neurological manifestations occur as painful episodes affecting the extremity and abdominal function, along with hypertension and hyponatremia and may result in respiratory failure and death. In hepatorenal tyrosinemia, the liver is mostly affected. The most frequent presentation is acute hepatic failure. Majority of deaths are caused by liver failure and hepatocellular carcinoma.

We report here a 4 months old infant who presented with abdominal mass and coagulopathy. He was diagnosed as tyrosinemia type 1 with associated hepatocellular carcinoma. This report also emphasizes the fact that tyrosinemia is one of the important causes of hepatocellular carcinoma in young infants.

CASE REPORT

A 4 month old infant, born of consanguineous parentage, presented with a right inguinal swelling along with fullness noted over the right side of the abdomen of two weeks duration. There was no history of sudden increase in size of the swelling or pain. There was no jaundice, high coloured urine, pale stools, bleeding manifestations, weight loss or fever. The mother had a history of hypothyroidism and was on thyroxine replacement. The baby was born preterm at 33 weeks by caesarean section.
and had a one week history of ICU care due to respiratory distress. He was developmentally normal for age. There was no history of infant or sibling deaths, chronic liver disease or malignancy in any of family members. The baby was immunised for age according to the national immunisation schedule. Clinical examination revealed an alert baby with normal vitals and no pallor, icterus or lymphadenopathy. Vitals were normal and there was no facial dysmorphism. There was an umbilical hernia and right sided inguinal hernia. Weight was 5.68 kgs (between 10th and 50th centile), while length was 56 cm (between 3rd and 10th centile). The head circumference was 42 cm (at 85th centile). Abdominal examination showed palpable liver 5 cm below the right costal margin. It was firm in consistency with sharp margins and a liver span of 8 cm. Spleen was palpable 4 cm below left costal margin, firm in consistency. There was also a right sided inguinal hernia. Cardiorespiratory and neurological examinations were unremarkable.

Investigations revealed mild anaemia, thrombocytopenia, mild direct hyperbilirubinemia, elevated liver enzymes, hypoalbuminemia and severe coagulopathy in the form of raised prothrombin time, hypofibrinogenemia and elevated D-dimer. The levels of alpha feto protein (AFP) was found to be significantly elevated (333071 units). There was no hypoglycemia and the renal function tests were normal. Peripheral smear showed normocytic, normochromic anaemia with thrombocytopenia. Urine for glucose and non-glucose reducing substances was positive. Blood gas analysis was normal. There were no features of rickets on X-ray. Ultrasonad abdomen showed multiple focal lesions in the liver and spleen with minimal ascites. He underwent a contrast enhanced CT of the abdomen which showed multiple hypodense cystic and solid lesions scattered across both lobes of liver with the solid components showing post contrast enhancement (Figure 1). The possibilities of mesenchymal hamartomas, hepatoblastoma, hepatocellular carcinoma, leukemia, storage disorder, hemochromatosis and neuroblastoma with metastasis were considered.

Ophthalmology evaluation showed no evidence of cataracts or cherry red spots.

In view of a history of consanguinity with acute hepatic failure, inborn errors of metabolism including galactosemia, hereditary fructose intolerance, tyrosinemia and glycogen storage disease type 3 and 4 with early onset cirrhosis were also considered. As there was no history of vomiting, hypoglycemia or cataract, galactosemia was less likely. Lipid profile was normal with no evidence of acanthocytes on peripheral smear. Bone marrow aspiration showed normo to hypocellular marrow with no blasts or abnormal cells and biopsy was normal. The patient underwent TMS, GCMS and testing for urine succinyl acetone. Urine GCMS showed elevated levels of succinyl acetone and 4-hydroxyphenylacetate which were in keeping with tyrosinemia. There was elevated succinyl acetone:creatinine ratio (90.21 micromol/l; normal <1). TMS showed elevated methionine (951.75 mmol/l). He was started on phenylalanine and tyrosine free special infant formula and oral nitisinone. As the platelets and coagulation factors were deranged, correction was done with vitamin K injections, serial FFPs and platelet transfusions. He subsequently underwent an ultrasound guided liver biopsy. The liver biopsy specimens showed features suggestive of hepatocellular carcinoma with glypican and AFP positivity (Figures 2-6).

Figure 1: Post contrast axial CT abdomen images showing multiple enhancing lesions in the liver.

Figure 2: 20x magnification of intact liver core showing delineated cellular areas with intervening hyalinized areas.

Figure 3: 100x magnification of hyalinized areas with dissecting tumor cells.
The parents were counselled regarding the nature of the disease, the need for compliance with dietary restriction and nitisinone treatment and the need for liver transplantation, if the response to nitisinone was unsatisfactory. Genetic testing and chemotherapy were offered, but not done due to lack of parental consent. He continued to have progressive deterioration of liver function and died of severe hepatic failure at an outside hospital, one month after the diagnosis.

DISCUSSION

Tyrosine is an amino acid which is obtained in the body from ingested proteins and is synthesised from phenylalanine. There are three main types of tyrosinemia. Tyrosinemia type I is a rare autosomal recessive disorder with clinical features involving multiple systems including the liver, kidney and peripheral nerves. These patients have a peculiar odour to the urine called a cabbage odour, presence of renal tubular dysfunction in the form of Fanconi’s syndrome and survive less than a year if untreated. Fulminant presentation with liver failure is common in the first few months of life. Tyrosinemia type II presents with skin lesions in the form of corneal ulcers and hyperkeratotic lesions of the digits, palms and soles, along with mental subnormality. Tyrosinemia type III causes intermittent episodes of ataxia with no hepatorenal involvement or skin lesions.

The enzyme whose deficiency leads to tyrosinemia type 1 is fumarylacetoacetate hydrolase. This enzyme is involved in the last step of tyrosine catabolism that involves cleavage of fumarylacetoacetate to fumarate and acetoacetate. Accumulation of fumarylacetoacetate occurs which leads to the clinical features. Fumarylacetoacetate is a strong alkylating agent and caused oxidative damage to hepatocytes and renal tubal cells. It is also a known mutagen, leading to the high incidence of hepatocellular carcinoma in these patients. These effects lead to chronic liver failure, hepatocellular carcinoma and renal tubular injury. Injury to the renal tubules results in aminoaciduria, glycosuria and phosphaturia causing renal tubular acidosis with hypophosphatemia and hypoproteinemia. Accumulated fumarylacetoacetate in the serum is rapidly metabolized to succinylacetoacetate which is then rapidly decarboxylated to succinylacetone. Increased levels of succinylacetone in serum and urine help in the diagnosis. It is succinylcholine in the urine that gives the characteristic boiled cabbage odour to the urine.

There may be acute, subacute and chronic forms of presentation based on the age. Acute presentation in children less than 6 months of age is the commonest, presenting with acute liver failure. The earlier the presentation, the graver the outcome. The mortality in patients who present below 4 months of age is more than 60% while it reduces to 4% in presentation after 6 months. Early presentations include bleeding manifestations like epistaxis and easy bruising while intracranial hemorrhages are uncommon. Subacute presentation is in infants between 6 and 12 months of age, as chronic liver and renal involvement. Renal manifestations include Fanconis syndrome with normal anion gap metabolic acidosis, hypophosphatemia and vitamin D resistant rickets. Chronic form presenting after one year can have various features including coagulopathy, liver disease, renal failure and neurological dysfunction including painful crises involving extremities or abdomen, raised blood pressure and polyneuropathy. Severe limb weakness may even necessitate mechanical ventilation.
Neonatal screening is done by detection of elevated levels of urinary succinylacetone. This is a very specific test for diagnosis of tyrosinemia and is a recommended neonatal screening tool. It is also a diagnostic test of choice for affected infants.

Management of patients includes dietary modification and restriction of food rich in phenylalanine and tyrosine. The compound 2-[2-nitro-4-trifluoromethylbenzoyl]-1, 3-cyclohexanedione (NTBC, nitisinone) is the treatment of choice. Nitisinone works by inhibiting the enzyme 4-hydroxy phenyl pyruvate dioxygenase which converts 4-hydroxy-phenylpyruvate to homogentisic acid thereby preventing the accumulation of a toxic metabolite, fumarylacetoacetate. NTBC therapy and dietary restriction together have shown to prevent development of chronic liver disease, renal tubular damage, hepatocellular carcinoma and the development of neurological complications and prevent development of hepatic and renal failure, early medical management can avoid hepatic and renal failure, neurological complications and prevent development of hepatocellular carcinoma. They also prevent the need for liver transplantation in many patients. Genetic counselling and screening of siblings is recommended in affected patients.

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