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Late Diagnosis of Hereditary Tyrosinemia Type I: The Case of Two First Cousins

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Abstract:- Hereditary Tyrosinemia Type I (HT1) is a rare metabolic disorder caused by a deficiency in fumarylacetoacetate hydrolase, leading to the accumulation of toxic metabolites and resulting in hepatic and renal complications. This case report details a 10-year-old patient from a consanguineous family with a significant history of hepatic failure due to hepatocellular carcinoma. The patient presented with abdominal pain, jaundice, and urinary abnormalities, which led to the diagnosis of HT1, confirmed by elevated succinylacetone levels. Despite initial treatment with nitisinone and a low-protein diet, surgical resection of the hepatic mass was impeded by vascular invasion, necessitating preoperative chemotherapy. This case underscores the importance of early detection and a multidisciplinary approach in managing HT1, highlighting ongoing research into advanced therapies and genetic interventions to improve patient outcomes.

I. INTRODUCTION

Hereditary Tyrosinemia Type I (HT1), also known as hereditary tyrosinosis, congenital tyrosinosis, or hepatorenal tyrosinemia, is a metabolic disorder resulting from a defect in the degradation of the amino acid tyrosine. The accumulation of metabolites upstream of the deficient enzyme, such as fumarylacetoacetate (FA), succinylacetoacetate, and succinylacetone (SA), leads to hepatic and renal toxicity. It is a rare inherited metabolic disorder with autosomal recessive transmission, and the measurement of succinylacetone is the golden test for diagnosis.(1,2)

We report the case of a 10-year-old child followed at the Rabat Children's Hospital, with a family history of a deceased first cousin who suffered from hepatic failure due to hepatocellular carcinoma. The urinary SA result indicating tyrosinemia was confirmed only in our patient.

II. OBSERVATION

The patient, Y, is a 10-year-old child from a first-degree consanguineous marriage, with a first cousin who was monitored since the age of 3 for rickets and died at age 5 from hepatic failure in the context of hepatocellular carcinoma. Y has been followed since the age of 6 at the Rabat Children's Hospital for hypophosphatemic rickets and has presented with abdominal pain, polyuria, and asthenia for the past 2 months. Physical examination revealed a distended abdomen with hepatosplenomegaly and jaundice. Biological investigations showed proximal tubulopathy, very high alpha-fetoprotein levels, and moderate hepatic cytolysis, but no signs of hepatic failure. Amino acid chromatography in blood and urine showed abnormal tyrosine levels with elevated succinylacetone in the urine. Radiological imaging included an abdominal CT scan showing a hepatic mass on a chronically diseased liver with portosystemic shunts and globular kidneys. Histopathological study of the hepatic mass biopsy was consistent with well-differentiated hepatocellular carcinoma.

Our patient was put on vitamin K, a low-protein diet, and nitisinone (NTBC) treatment at a dose of 2 mg/kg/day. Surgical resection of the hepatic carcinoma was initially impossible due to vascular invasion, and preoperative chemotherapy was recommended in this context.

III. DISCUSSION

Tyrosinemia Type I (TYR1) is a hereditary metabolic disorder caused by a deficiency in fumarylacetoacetate hydrolase (FAH), a key enzyme in the degradation pathway of the amino acids tyrosine and phenylalanine. This deficiency leads to toxic accumulation of fumarylacetoacetate and maleylacetoacetate, resulting in severe liver damage, hepatic failure, and sometimes neurological complications.(3,4)

The clinical manifestations of TYR1 often appear within the first few months of life. Typical symptoms include hepatomegaly, cirrhosis, coagulation disorders, and vomiting episodes. Early detection is crucial as timely treatment can significantly improve outcomes. Diagnosis is based on biochemical tests showing elevated levels of tyrosine and associated metabolites, as well as genetic tests to confirm mutations in the FAH gene.(4,5,6)

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The treatment of TYR1 has evolved over the past decades. Historically, the main treatment was dietary restriction of tyrosine and phenylalanine, combined with medications to manage symptoms. However, liver transplantation is often necessary for severe cases, providing a chance for a cure by replacing the defective liver with a functional one.(7)

Early treatment with 2-(2-nitro-4-trifluoromethylphenyl) thiazole can reduce the toxicity of accumulated metabolites and improve patients' quality of life. Combined strategies, such as transplantation and drug therapy, may offer a more effective approach to managing this complex condition.(8,9)

Ongoing research in the field of TYR1 focuses on developing gene therapies and new pharmacological strategies for more targeted and less invasive treatment. (10,11)Gene therapy, in particular, shows significant potential for correcting the genetic mutations responsible for the disease at its source. Additionally, advancements in newborn screening techniques allow for earlier detection, which could transform disease management and reduce severe complications.(12,13)

IV. CONCLUSION

Tyrosinemia Type I remains a complex disease requiring a multidisciplinary approach for diagnosis, treatment, and long-term management. Continuous progress in research and treatment development offers new hope for patients and their families. Appropriate management, coupled with regular monitoring, is essential to optimize outcomes and improve the quality of life for individuals affected by this rare but serious condition.(13)

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ICONOGRAPHY

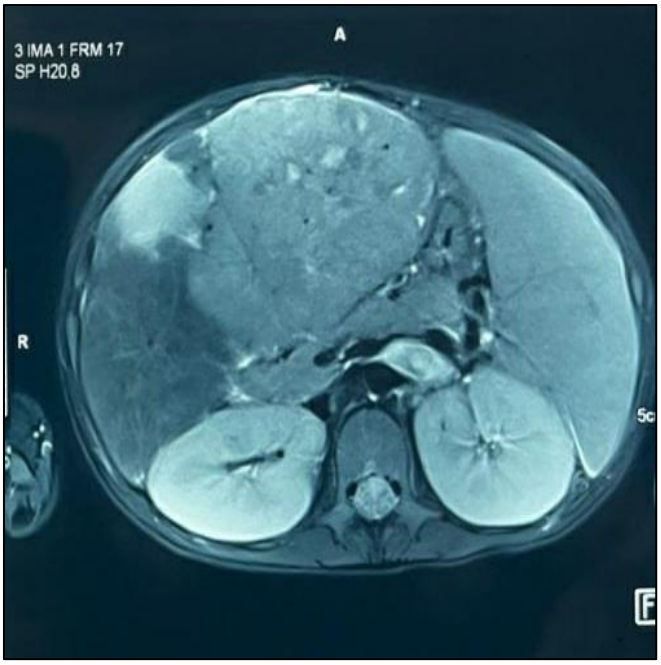

Fig 1: Abdominal CT Scan: Intra-Abdominal Mass Appearing to be Dependent on the Liver with Signs of Portal Hypertension and Enlarged Kidneys with Hypodense Infiltrations.

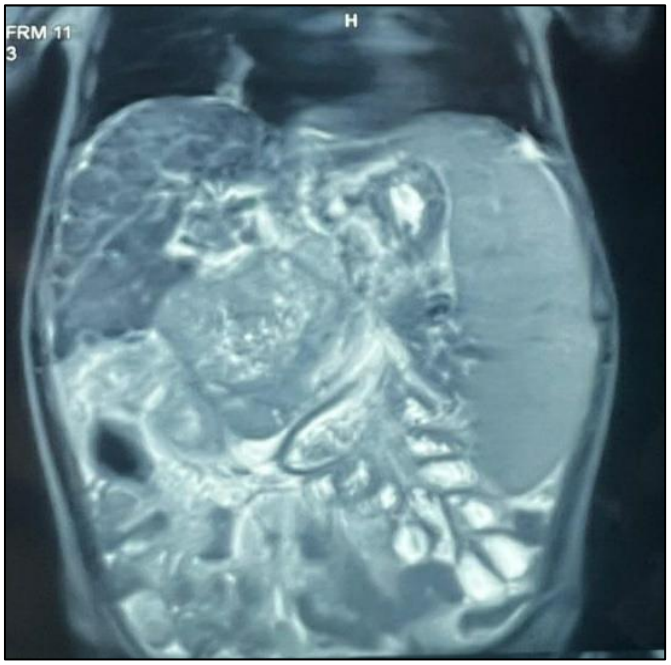

Fig 2: Hepatic MRI: Hepatic Mass on a Liver with Chronic Liver Disease, with Porto-Systemic Shunts and Globular Kidneys.