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Case Report

A Giant Hepatocellular Carcinoma Complicating Hereditary Tyrosinemia Type 1: A Pediatric Case Report with a Literature Review

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Received: February 24, 2025; **Published:** September 04, 2025

Abstract

Hereditary tyrosinemia type 1 (HT1) is a rare metabolic disorder that predisposes patients to hepatocellular carcinoma (HCC) in cases of delayed diagnosis or inadequate treatment. We report the case of a 9-year-old boy with HT1, initially started on treatment but lost to follow-up. He presented with growth retardation and a large hepatic mass, later confirmed as HCC. This case highlights the critical importance of early diagnosis, continuous treatment, and regular monitoring to prevent severe complications of HT1.

Keywords: *Hereditary Tyrosinemia Type 1; Hepatocellular Carcinoma; Alpha-Fetoprotein; Liver Transplantation*

Introduction

Hereditary tyrosinemia type 1 (HT1) is a rare autosomal recessive metabolic disorder caused by a deficiency of fumarylacetoacetate hydrolase, leading to the accumulation of toxic metabolites [1-3]. Although rare, this condition is associated with severe complications, particularly the early development of hepatocellular carcinoma (HCC) [4,5]. With the introduction of nitisinone, a 4-hydroxyphenylpyruvate dioxygenase inhibitor, combined with dietary restriction of tyrosine and phenylalanine, the natural history of the disease has significantly improved, reducing morbidity and delaying the onset of HCC [6,7]. However, gaps in early diagnosis, treatment adherence, or regular monitoring increase the risk of severe complications. This case report provides a striking example of this dynamic and underscores the importance of rigorous management in pediatric metabolic disorders.

Case Report

A 9-year-old boy, followed since the age of 3 for rickets, was diagnosed at the age of 6 with hereditary tyrosinemia type 1 (HT1). The diagnosis was established based on an abnormally elevated alpha-fetoprotein (AFP) level and blood tests confirming tyrosinemia. He was started on treatment, including a strict dietary regimen and medical management. However, the patient was lost to follow-up for three years and returned with complaints of significant growth retardation (height below -3 standard deviations), persistent bone pain, and marked abdominal distension.

On clinical examination, significant hepatosplenomegaly and generalized growth retardation were observed. Laboratory tests revealed hypochromic microcytic anemia (hemoglobin 8 g/dL), elevated bilirubin levels, normal coagulation parameters, and a markedly elevated AFP level.

Abdominal ultrasound showed an enlarged liver with irregular contours and nodular architecture, hypertrophy of segment I, and atrophy of segment IV. A large heterogeneous mass extending to the umbilicus was identified, but its precise origin was indeterminate. Homogeneous splenomegaly was also noted.

An abdominal computed tomography (CT) scan was performed for further evaluation. It revealed an intraperitoneal mass located in the supramesocolic region, appearing to arise from liver segments IV and III, with a "claw sign." The mass was well-defined, multilobulated, and measured 110 × 96 × 94 mm. Post-contrast imaging demonstrated heterogeneous enhancement with central necrotic areas. Vascularization of the mass was noted, supplied by branches of the right hepatic artery.

For more precise characterization, a hepatic MRI was performed. It confirmed the presence of a well-defined, lobulated, roughly oval intraperitoneal mass measuring 128 × 109 × 87 mm. The mass was connected to the liver with a smooth interface, showing isointense signals on T1-weighted images and heterogeneous signals on T2-weighted images, with hyperintense T2 areas and restricted diffusion. After gadolinium administration, the mass demonstrated mild arterial-phase enhancement, washout during the delayed phase, and a persistently enhanced peripheral capsule. Non-enhancing central necrotic zones were also noted. The mass displaced adjacent structures without invading them, including the anterior abdominal wall, pancreas, duodenum, lesser gastric curvature, and transverse colon.

Other findings included an enlarged dysmorphic liver with regenerative nodules in segments V (14 × 17 mm) and VII (14 × 10 mm), homogeneous splenomegaly (FS = 19 cm), portosystemic shunts around the stomach with recanalization of the umbilical vein, and mild intraperitoneal effusion. Additionally, the kidneys were enlarged with diffuse infiltrates showing isointense signals on T1- and T2-weighted images and no contrast enhancement, consistent with metabolic renal involvement.

The clinical, biological, and radiological findings were consistent with a diagnosis of hepatocellular carcinoma (HCC) arising in a dysmorphic liver in the context of chronic HT1. A biopsy of the hepatic mass confirmed the diagnosis of HCC, grade II Edmondson-Steiner (moderately differentiated, according to WHO criteria) (Figure 3). The case was discussed in a multidisciplinary team meeting, and liver transplantation was recommended.

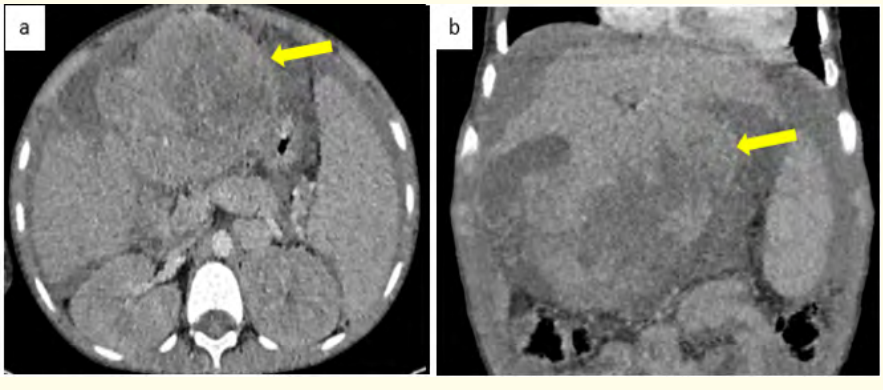
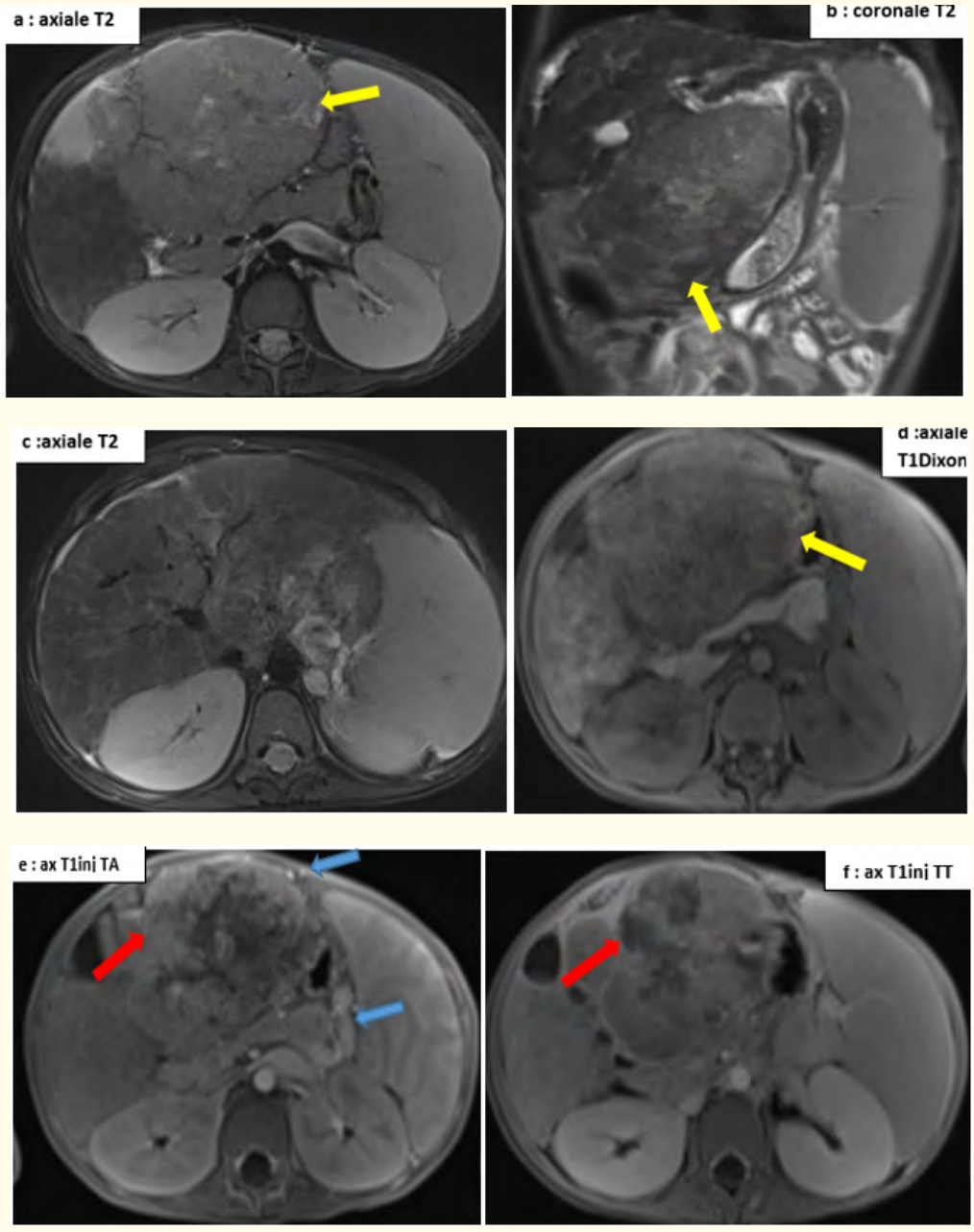


Figure 1: *Contrast-enhanced abdominal-pelvic CT scan. Axial plan (a) and coronal reconstruction (b). Intraperitoneal mass in the supramesocolic region, appearing to originate from the liver (smoothly connected to hepatic segments IV and III with a claw sign). The mass is relatively well-defined, multilobulated, and has soft tissue density with heterogeneous enhancement after contrast injection, containing central necrotic areas (yellow arrow). Associated findings include a dysmorphic liver with irregular contours, splenomegaly with portosystemic shunting, and mild intraperitoneal effusion.*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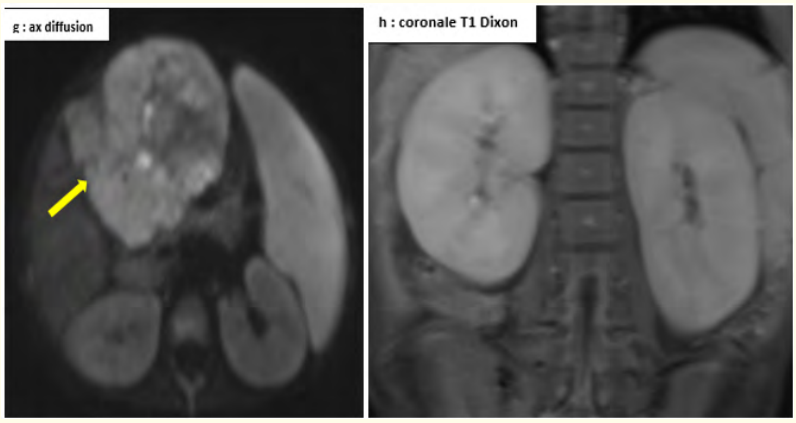
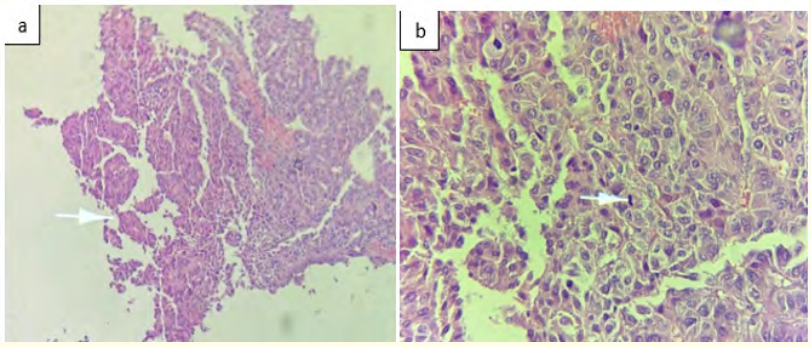


Figure 2: *Hepatic MRI. Axial T2 sequences (a and c), coronal T2 sequence (b), axial T1 Dixon (d), coronal T1 Dixon (h), and contrast-enhanced axial T1 sequences: arterial phase (e) and delayed phase (f), diffusion b800 (g).*

The intraperitoneal mass (yellow arrow) is roughly oval, relatively well-defined, with lobulated contours. It appears to originate from the liver, connecting smoothly with hepatic segments IV and III (claw sign). The mass shows isointense T1 signal, heterogeneous T2 signal with hyperintense T2 areas, and restricted diffusion. After gadolinium injection, it demonstrates mild enhancement during the arterial phase with washout in the delayed phase (red arrow), central non-enhancing necrotic zones, and a persistently enhanced capsule in the delayed phase. The liver is enlarged (vertical height = 11 cm), irregular, and dysmorphic, with hypertrophy of segment I and hypotrophy of the right lobe, especially segment IV. The segment IV region exhibits heterogeneous appearance with hypointense T1 and T2 bands that homogenize in the delayed phase, causing capsular retraction (c). Multiple nodular signal abnormalities are noted, showing hypointense T1 and T2 signals with mild portal phase enhancement but no washout, suggestive of regenerative nodules. The spleen is enlarged (vertical size = 19 cm) without focal lesions (b). Splenic and perigastric portosystemic shunts are observed, along with recanalization of the umbilical vein (blue arrows). A thin layer of intraperitoneal fluid is seen around the liver, spleen, bowel loops, and within the lesser sac. The kidneys are enlarged, with diffuse infiltrates showing isointense T1 and T2 signals and no contrast enhancement (h).



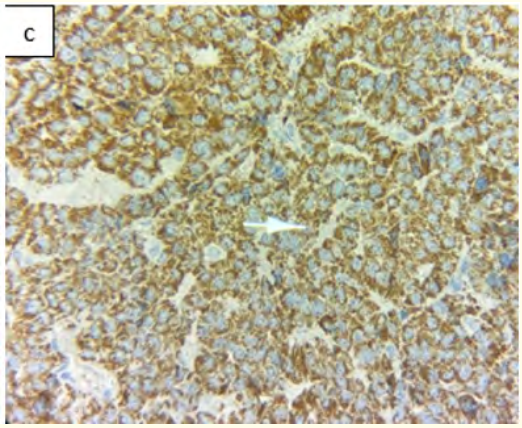


Figure 3a-3c: *(a) Microscopic examination reveals a tumoral proliferation arranged in trabeculae and pseudoglandular (acinar) structures. (b) The tumor cells are polygonal, exhibiting anisokaryosis with hyperchromatic, nucleolated nuclei, numerous mitotic figures, and moderate amounts of eosinophilic or clear cytoplasm. (c) Immunohistochemical analysis shows intense granular cytoplasmic staining with anti-Hepatocyte Paraffin 1 (Hep Par), confirming the diagnosis of hepatocellular carcinoma, grade II Edmondson-Steiner (moderately differentiated, according to WHO classification).*

Discussion

Hereditary tyrosinemia type 1 (HT1, OMIM 276700) is an autosomal recessive disorder caused by a deficiency of fumarylacetoacetate hydrolase (FAH), a key enzyme in the metabolism of tyrosine [1-4,6]. This deficiency, resulting from mutations in the FAH gene located on locus 15q23-q25, leads to the accumulation of toxic metabolites such as fumarylacetoacetate (FAA), succinylacetone (SA), and succinylacetoacetate (SAA) [1-3,9]. These metabolites cause progressive damage to the liver, kidneys, and, in some cases, the nervous system [1-3,9].

FAA, the main toxic metabolite, induces oxidative stress within hepatocytes and renal cells by interacting with glutathione and sulfhydryl proteins, leading to chromosomal instability, cell cycle arrest, and apoptosis. These mechanisms promote the progression to liver cirrhosis and hepatocellular carcinoma (HCC). Furthermore, the accumulation of FAA inhibits the activity of tyrosine aminotransferase (TAT), raising tyrosine levels [9,13]. The metabolites SA and SAA, essential diagnostic markers, are used in newborn screening (NBS) programs for early detection [9,13].

The global incidence of hereditary tyrosinemia type 1 (HT1) is estimated at 1 in 100,000 live births, but it is significantly higher in certain regions, particularly in Saguenay-Lac-Saint-Jean (Quebec, Canada) with 1 in 1,846 births, as well as in Norway and Finland [5,9].

Hereditary tyrosinemia type 1 (HT1) is a rare disorder that typically manifests before the age of 2, often through acute liver failure or renal and neurological involvement. Chronic forms include Fanconi syndrome, cirrhosis, hypophosphatemic rickets, and growth retardation. Isolated signs, such as coagulopathy, may appear after the age of 2 (1.5-7.9). Our patient presents with a chronic form involving hepatorenal impairment, rickets, and growth retardation.

The diagnosis is based on the detection of succinylacetone (SUAC) in the blood or urine, a pathognomonic marker often used in newborn screening [8]. Biological abnormalities include a moderate elevation of tyrosine, methionine, phenylalanine, and alpha-fetoprotein (AFP) [8,9].

Newborn screening, available in some countries like the United States, allows for early diagnosis, although its absence in many regions often delays management [9]. This was the case for our patient.

The monitoring of patients with hereditary tyrosinemia type 1 (HT1) relies on abdominal imaging, primarily through ultrasound, to screen for liver nodules and exclude hepatocellular carcinoma (HCC). In the presence of a nodule, MRI is recommended to further characterize it, as HCC is a common complication with a lifetime risk estimated at 37% [6,7,9,10]. Nodules should be managed promptly, even without formal evidence of malignancy [7,10].

Hepatocellular carcinoma (HCC) may present with symptoms such as fatigue, abdominal pain, or hepatic bleeding, but it is often detected before the appearance of these signs through imaging and biological testing [13]. Alpha-fetoprotein (AFP) is a key marker for the diagnosis and monitoring of HCC. In untreated HT1 infants, AFP levels remain elevated during the first year but decrease rapidly with NTBC treatment combined with a low-tyrosine diet, typically normalizing within 12 to 24 months [7,10]. However, AFP lacks specificity and may remain normal in certain cases of HCC, necessitating the identification of alternative markers such as lectin-reactive alpha-fetoprotein, whose utility requires further validation [7,10,13].

Imaging in HT1 patients often reveals signs of cirrhosis, including hypertrophy of the caudate lobe and lateral segments of the left lobe, atrophy of the posterior segments of the right lobe, a nodular liver surface, parenchymal heterogeneity, and signs of portal hypertension such as splenomegaly, portosystemic collaterals, and ascites [13].

Ultrasound remains the preferred tool for initial screening due to its availability, safety, and non-invasive nature. Its sensitivity for diagnosing HCC ranges from 60% to 80%, depending on the operator's expertise. Doppler imaging can enhance this sensitivity by detecting high-velocity arterial flow in suspicious lesions [13].

Imaging plays a crucial role in monitoring and diagnosing liver lesions in patients with hereditary tyrosinemia type 1 (HT1). MRI offers high sensitivity (89 - 100%) for detecting hepatocellular carcinoma (HCC), particularly for small lesions measuring 1 - 2 cm. It allows for precise characterization through T1- and T2-weighted sequences and dynamic acquisitions, where HCC demonstrates arterial enhancement followed by venous washout, delayed capsular enhancement, and diffusion restriction on DWI images. Regenerative and dysplastic nodules are distinguished by the absence of these features [7,10].

Although less frequently used, computed tomography (CT) is useful for assessing specific characteristics of HCC, such as heterogeneity due to fat or necrosis, and provides results comparable to MRI in dynamic phases.

Ultrasound remains the primary modality for routine surveillance, despite its variable sensitivity (60 - 80%) influenced by the operator. Complementary Doppler imaging assists in detecting abnormal arterial flow in suspicious lesions. However, for HT1 patients, MRI is essential to confirm the nature of suspicious lesions and monitor nodules with malignant transformation potential. Studies by Ozcan., *et al*. and van Ginkel., *et al.* highlight cases of HCC without elevated AFP, underscoring the critical role of MRI [10,12].

The LI-RADS system, commonly used to standardize interpretation in at-risk adults, is not validated for pediatric patients, complicating diagnosis in children [10]. Reports of "silent" HCC cases, such as those described by Castilloux., *et al*. emphasize the importance of rigorous surveillance, particularly in low-resource settings where diagnostic delays negatively impact clinical outcomes, as noted by Palaniappan., *et al.* [5,11].

Hepatocellular carcinoma (HCC) frequently develops in a cirrhotic liver. Small lesions (< 2 cm) are typically well-differentiated, composed of hepatocytes arranged in trabecular or acinar patterns, while more advanced lesions exhibit thickened trabeculae due to clonal dedifferentiation [7]. Our case is notable for the massive size of the HCC.

The treatment of hereditary tyrosinemia type 1 (HT1) has been revolutionized by neonatal screening and the early initiation of nitisinone (NTBC). This therapy blocks the enzyme hydroxyphenylpyruvate dioxygenase (HPD), preventing the formation of toxic metabolites and reducing hepatic and renal complications, including the risk of HCC. When initiated early, within the first weeks of life, this treatment nearly eliminates the need for liver transplantation [7,9].

However, despite therapeutic advances, the risk of HCC persists, particularly in patients treated later in the disease course [14]. Rigorous surveillance is essential and includes regular alpha-fetoprotein (AFP) measurements and imaging studies such as ultrasound and MRI. Any AFP elevation or the emergence of hepatic nodules on imaging should be addressed, even in the absence of AFP changes [6,9,13]. Early detection of hepatic lesions through stringent monitoring improves clinical outcomes [11].

NTBC treatment can lead to elevated serum tyrosine levels, necessitating strict dietary restrictions to prevent complications such as corneal ulcers and neurodevelopmental disorders. In cases where treatment fails or HCC develops, orthotopic liver transplantation remains the only curative option [14]. Van Spronsen., *et al*. reported a case of a child who developed HCC despite medical therapy, with liver transplantation being the treatment of choice [14]. While post-transplant survival rates are high (90%), limited access to this treatment in certain regions and the high cost of NTBC present significant barriers [11,13].

Experimental approaches such as gene therapy and the use of stem cells aim to replace hepatocytes deficient in fumarylacetoacetate hydrolase (FAH), though these strategies are not yet clinically applicable [7]. These innovations could potentially transform the treatment landscape for HT1 in the future.

Conclusion

Hepatocellular carcinoma (HCC) is a serious complication of hereditary tyrosinemia type 1 (HT1), but it can be prevented through early diagnosis, appropriate treatment, and rigorous follow-up. This case underscores the importance of systematic monitoring in HT1 patients, including regular biological assessments, imaging studies, and evaluation of oncogenic risk factors. Liver transplantation remains a critical therapeutic option when HCC is diagnosed at an advanced stage.

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Volume 8 Issue 10 October 2025