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Teenage Girl with Tyrosinemia Type 1 Masquerading as Hepatic Insufficiency: A Rare Case Report

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Abstract **Case Report**

***Background*:** Tyrosinemia type 1 (TT1) is an autosomal recessive disorder caused by deficiency of the enzyme fumarylacetoacetate hydrolase (FAH). Because of this defect, toxic metabolites like are formed and they can cause severe disruption of intracellular metabolism of the kidney and liver. HT1 can manifest at any age from infancy to adulthood and is characterized, if untreated, by progressive liver impairment and increased risk of hepatocellular carcinoma. ***Case Report*:** In this case, we provide a rare occurrence of Tyrosinemia type 1 at the stage of liver cirrhosis, in a 16-year-old Moroccan girl. At the age of 10, she had a follow-up due to growth failure. The clinical and biochemical factors coincided to indicate the presence of hypophosphatemia rickets, a condition often linked to Tyrosinemia type I. Regrettably, due to a delayed diagnosis of Tyrosinemia, the patient succumbed to abrupt and severe hematemesis. ***Conclusion*:** We report the first case in the literature of Tyrosinemia type 1 manifesting as hepatic insufficiency at a very late age. We strongly believe that the poor prognosis in our case was due to a delay in diagnosis and essentially to the lack of knowledge of this rare entity in our context.

Keywords: Tyrosinemia Type 1, Hepato Cellular Insufficiency, Liver Failure, Hypophosphatemia Rickets.

INTRODUCTION

Hereditary type 1 Tyrosinemia (HT-1) is a rare autosomal recessive inherited metabolic disease of Tyrosine metabolism caused by the deficiency of fumarylacetoacetate hydrolase, a key enzyme in the final step of tyrosine metabolism [1]. The clinical presentation of HT1 is widely variable, and affected individuals can manifest the disease from infancy to adulthood, although presentation after 2 years is rare.

We present a perplexing case of Tyrosinemia type 1 with hypophosphatemic rickets revealed by hepatic insufficiency in a 16 years old Moroccan girl.

CASE REPORT

A 16-year-old female patient with no previous pathological history was admitted to our department in July 2021 for moderate hematemesis and melena preceded by 1 month history of atypical right hypochondrium pain. The patient was the eldest of two siblings from a first-degree consanguineous marriage. She was seeing a doctor for a stature and weight delay since the age of ten with no identifiable cause.

On arrival, the patient was conscious with a Glasgow score of E4V5M6 and her body temperature was 37°, her blood pressure was 120/80mmHg with a heart rate of 79 bpm and a respiratory rate of 20cpm. The physical examination showed significant facial and conjunctival pallor, a sharp-edged hepatomegaly with a hepatic arrow of 18cm, with a splenomegaly without collateral circulation or dullness. She had a height of 135 cm and a weight of 49 kg (body mass index of 26,9).The osteoarticular examination revealed signs of rickets such as: enlargement of the wrists, varus deformity of the lower limbs (Fig. 1), sternal protrusion with an aspect of a carina thorax.

Biologically, she had a normochromic normocytic anemia with a hemoglobin at 9g/dL with a low platelet count of 75,000 and normal white blood cell count at 8,500, with both low prothrombin rate of 40 % and albumin at 20. Renal function and Ionogram were within normal limits and she had moderately elevated transaminases.

In the setting of gastrointestinal bleeding, the patient had an esophagogastroduodenoscopy (EGD) procedure. The EGD showed grade 3 esophageal varices with red symptoms and gastropathy caused by portal

hypertension. The ligation of the esophageal varices was carried out smoothly and without any complications. The patient had an abdominal ultrasound that revealed a liver with an irregular texture and an enlarged spleen, as well as a dilated portal vein measuring 18 mm. No nodular lesions were detected. Multiple tests have been conducted to ascertain the cause of liver lesions, although no evidence has shown the presence of a viral, autoimmune, or alpha antitrypsin deficiency. Wilson's disease and hemochromatosis have also been excluded as potential causes.

Based on the bone deformations, a phosphocalcic evaluation was conducted. The results showed a normal level of calcium at 90, a low level of phosphorus at 20, and a deficit of vitamin D at 9. The level of parathyroid hormone (PTH) was within the normal range. These findings validate the diagnosis of hypophosphatemic rickets.

The coexsistence of cirrhosis and hypophosphatemic rickets aroused suspicion of type 1 Tyrosinemia. Moreover, the Level of alpha foeto protein (AFP) was high at 20,000 which prompted further investigation for this diagnosis. Both urinary and plasma succinylacetone (SA) were elevated (2196 nmol/mmol creatinine [normal 0-28] and 60 nmol/L [normal 0-21], respectively. These findings were pathognomonic of type 1 Tyrosinemia. The patient was a perfect candidate for Nitisinone, unfortunately she passed away as a result of sudden severe hematemesis.

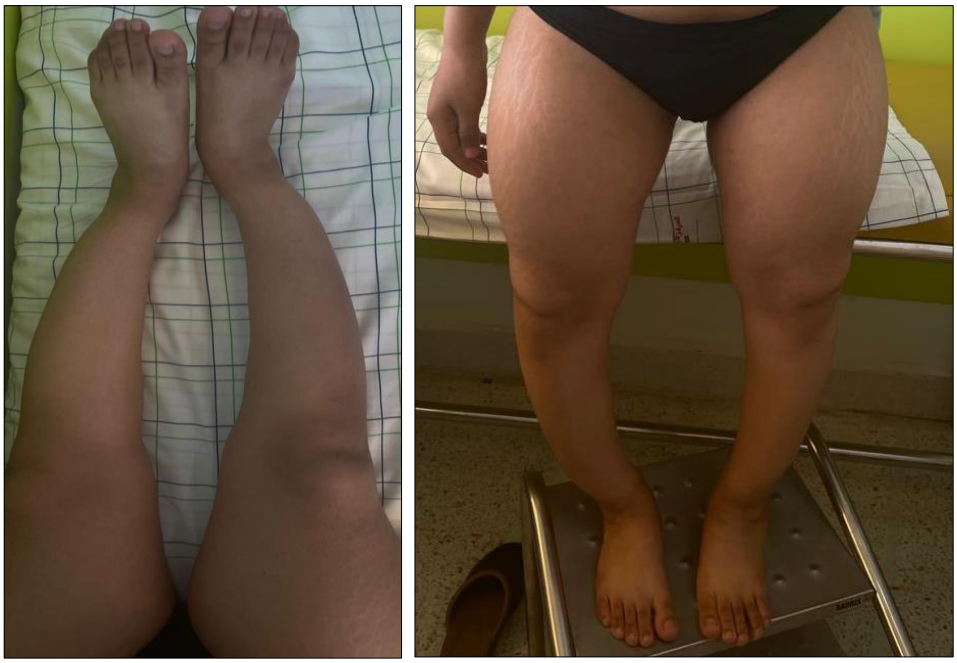

Figure 1: Varus deformity of the legs

DISCUSSION

Hereditary type 1 tyrosinemia (HT1) is a rare inherited autosomal recessive disorder of tyrosine metabolism, characterized by progressive liver damage, dysfunction of kidney tubules, and neurological crises, with a long-term risk of hepatocellular carcinoma [3]. The mechanism of this disease comprises a deficiency of FAH, leading to the accumulation of toxic intermediate metabolites of tyrosine breakdown, in liver and kidney cells, causing cellular damage [4].

According to the literature, HT1 can occur at any age, from infancy to adulthood, and has a broad spectrum of clinical symptoms. The gravity of the disease generally inversely correlates with the age of onset. HT1 is categorized into three types according to the level of liver function damage: acute, sub-acute and chronic, although there are no clear dividing lines between these three types. [5].

Our report showcases a patient with a chronic type of HT1, since the patient had a follow up for growth delay since the age of ten. However, at that time, no examinations assessing the patient's liver condition were performed. The diagnosis of HT1 was not made until the age of sixteen year old when she was found to have advanced cirrhosis with rapidly progressive liver failure and clinical signs of rickets.

It is crucial to have a functional universal newborn screening program for tyrosinemia in order to make an early diagnosis. In countries where testing for tyrosinemia is part of routine newborn screening, HT1 is usually identified before the onset of symptoms, often by the age of one month [6]. However, in many countries around the world, including in Morocco, where this condition is not part of the newborn screening program, HT1 is only diagnosed when clinical signs of organ failure become apparent.

A significantly high AFP level in the blood is usually seen in patients, especially the acute presentation of the disease, nevertheless AFP levels could be within normal range in those with the chronic form. An elevated AFP level alone is not sufficient to diagnose of HT1; however, on the other hand, an increased SA level in the blood or urine is pathognomonic of HT1 [7].

Experts in this field emphasize that treatment with the drug Nitisinone, also known as 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione (abbreviated as NTBC), at a dose of 1 mg/kg/day should be initiated upon suspicion of HT1, in addition to a diet low in phenylalanine/tyrosine [8]. The response to this drug is typically rapid, with clinical improvement occurring within one week [4-9].

CONCLUSION

To summarize, this is the first instance in Morocco of a patient with an atypical delayed manifestation of HT1. Early diagnosis of HT1 is crucial in order to significantly minimize or eradicate its complications. Early diagnosis and prompt beginning of therapy with Nitisinone, together with adherence to a balanced diet, improve immensely the patient's outcomes.

Conflicts of Interest: None

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