Hepatocellular Carcinoma in Tyrosinemia Type 1 Without Clear Increase of AFP

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Patients with hereditary tyrosinemia type 1 have an elevated risk of developing hepatocellular carcinoma, especially if initiation of treatment with 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanediene is delayed. Hepatocellular carcinoma can usually be suspected when there are increased $\alpha_1$-fetoprotein levels and characteristic imaging features. The present case shows that a lack of a clear increase in $\alpha_1$-fetoprotein should still lead to consideration of liver transplantation when imaging features change.

Hereditary tyrosinemia type 1 (HT1; McKusick 276700) is a metabolic disease in the catabolic pathway of tyrosine. HT1 is based on functional fumarylacetoacetate hydrolase deficiency, causing liver failure, hepatocellular carcinoma (HCC), renal tubulopathy, glomerular disease, heart disease, and neurologic problems. Treatment of HT1 patients with 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanediene (NTBC) inhibits the upstream enzyme 4-hydroxyphenylpyruvate dioxygenase, thereby preventing the formation of the toxic metabolites fumarylacetoacetate and succinylacetoacetate. Liver failure, renal disease, heart disease, and neurologic problems are resolved with treatment.1,2

Since the introduction of NTBC in 1992, the incidence of HCC in HT1 patients treated with NTBC has dramatically decreased compared with reports in patients treated without this agent.1–4 However, NTBC-treated patients with HT1 are at increased risk of developing HCC.5,6 Patients with a late initiation of NTBC due to delayed diagnosis or unavailability of NTBC, a slow decrease of $\alpha_1$-fetoprotein (AFP), or an AFP level that remains just above the normal range of 0 to 10 $\mu g/L$ have an increased risk of developing HCC.3,5–7

In HT1, early detection of HCC is based on routine follow-up of AFP levels and liver imaging. An increase in AFP after the start of NTBC suggests the development of HCC. To our knowledge, the present case report is the first analysis of a patient with HT1 in whom HCC was found without a clear increase in AFP levels and with hepatic lesions that were not suspicious for HCC.

CASE REPORT

A white female child presented with delay in gross motor development at 14 months of age.6 She had hypotonia, an enlarged abdomen due to hepatosplenomegaly, and rickets. Laboratory investigations showed a blood tyrosine level of 335 $\mu mol/L$, an AFP level of 528 568 $\mu g/L$, and a urinary succinylacetone concentration of 148 mg/mmol of creatinine. DNA analysis revealed homozygosity for the common mutation (IVS12+5[g>a]). NTBC was initiated at a dose of 1.2 mg/kg with a diet restricted in phenylalanine and

abstract

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Mr van Ginkel completed the initial version of the manuscript and revised the manuscript; Dr Gouw was responsible for the histopathologic examination of the patient’s liver and critically reviewed the manuscript; Dr van der Jagt performed the radiologic follow-up of the patient and critically reviewed the manuscript; Dr de Jong performed the patient’s liver transplantation and critically reviewed the manuscript; Dr Verkade critically reviewed the manuscript; and Dr van Spronsen was responsible for the diagnosis of hereditary tyrosinemia type 1, performed the treatment and monitoring of the patient, drafted the initial version of the manuscript, and cowrote the manuscript. All authors approved the final manuscript as submitted.


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tyrosine. The patient’s condition was stable during the following years. Her AFP levels decreased slowly, blood and urinary succinylacetone concentrations remained within the normal range, and NTBC concentrations were continuously within the therapeutic range (60–80 μmol/L), except for 2 occasions when concentrations were slightly lower (40–50 μmol/L). Regular, 4 times yearly, ultrasound/computed tomography (CT) scans were conducted and revealed no hepatic nodules suspicious for HCC. After ~4 years of NTBC treatment, a hepatic lesion of 8 × 6 mm was found on ultrasound and interpreted as a hemangioma. At that time, AFP concentrations had stabilized around 24 μg/L (Fig 1), whereas a further decrease was expected. More specific characterization of the lesion was performed by using multiphase contrast-enhanced CT scanning. The scans revealed 2 lesions (15 × 15 mm each), with no arterial enhancement and with hypodensity in the venous phase. Based on these characteristics, the lesions were considered to be hyperplastic nodules rather than foci of HCC. An ultrasound of the liver revealed no increase in the number or size of the lesions; treatment with NTBC was again monitored closely to exclude the possibility of nonoptimal treatment. After 10 months, MRI was performed as a more objective follow-up measurement. The lesions were still visible in contrast to ultrasound and MRI, now, 6 focal lesions with a diameter up to 15 mm were found; there was no arterial enhancement, portal venous washout, or different retention in the hepatic phase. On the basis of these characteristics, the lesions were interpreted as hyperplastic nodules (Fig 2). At the time of the MRI, AFP levels had not decreased to normal values (0–10 μg/L) and were recorded as 27.7 μg/L (Fig 1).

The patient was listed for liver transplantation due to the following reasons: (1) a new lesion representing a hemangioma at this age is curious; (2) the AFP levels had not decreased further; and (3) we were unable to exclude the possibility of HCC on imaging. After a 3-month wait time, the liver transplantation was performed; the patient was 6.5 years of age. At the time of transplantation, the serum AFP concentration was 26 μg/L (Fig 1). The removed liver showed cirrhosis with 7 distinguishable focal lesions. The lesion first considered as a hemangioma was now interpreted as “a lesion compatible with early HCC” (not shown), whereas the second lesion, first noted on the CT scan, was diagnosed as HCC (Fig 3). Both lesions were 9 mm in diameter. The other 5 lesions, all with a diameter of 3 to 10 mm, were interpreted as focal lesions displaying small cell dysplasia. During the 8-year follow-up after liver transplantation, there were no signs of metastases, and AFP concentrations remained within the normal range.

**DISCUSSION**

HT1 is associated with an increased risk of developing HCC. Signs suggestive of HCC in the individual HT1 patient are a slow decrease to normal in AFP values; AFP not reaching normal values; an increase in AFP levels; and/or a new lesion found on imaging. In other diseases with a high risk of developing HCC (eg, hepatitis B and C), up to 44% of patients diagnosed with HCC show no clear increase in AFP levels. Until now, all reported HT1 patients with proven HCC had exhibited a well-defined rise in AFP levels and a clear lesion at imaging. Therefore, AFP in HT1 has always been considered a reliable marker for HCC development. However, the present report is based on 1 patient. In addition, we do not know what would have happened if we had chosen a “wait and see” approach. It is possible that >1 year after the first detection, the AFP levels would eventually have started to rise given the pathologic report of early-stage HCC.

Theoretically, the malignancy could also have been a hepatoblastoma, which may present without increased AFP levels and has been reported at least once in HT1. The pathology of the explanted liver, however, clearly showed HCC. In the present case report, AFP levels at the time of HT1 diagnosis at age 14 months was 528 568 μg/L. AFP levels may be high in infancy even when the child is healthy, but this scenario especially refers to neonatal age and the first 6 months of life. Indeed, AFP levels at diagnosis in this patient may have been very high for her age. However, until now, it has

![Figure 1](http://pediatrics.aappublications.org/)

**Figure 1**

Course of AFP from diagnosis until 1 year after liver transplantation. After an initial decline in AFP levels stabilized at ~25 μg/L. After liver transplantation, AFP levels further decreased to normal values. This finding is in contrast with the reference patients who almost immediately reached normal values (ie, 0–10 μg/L).
been unclear whether there is a relation between the AFP level at time of HT1 diagnosis and the risk of HCC development and whether AFP at time of diagnosis may be a useful additional sign suggesting an increased risk of HCC development in the individual HT1 patient.

Imaging, especially CT and/or MRI with contrast, plays a key role in the (early) diagnosis of HCC. In general, HCC has a characteristic pattern in various imaging modalities, although differentiating HCC from other lesions remains challenging. In the present case, for example, both CT and MRI results suggested hyperplastic nodules rather than HCC.

**CONCLUSIONS**

We present a case illustrating that AFP levels, ultrasound, CT, and MRI may fail to detect early HCC in patients with HT1. Based on the data

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**FIGURE 2**

MRI of the liver. A and C, The lesion in segment 5 is slightly lower in intensity on T1 (arrow); B, the lesion is not visible on the T2 half-Fourier single-shot turbo spin-echo sequence; D, the lesion shows no arterial enhancement; E, the lesion is not visible in the portal venous phase; and F, the lesion is slightly lower in intensity in the parenchymal phase after administration of the liver-specific contrast agent.

**FIGURE 3**

HCC in the native liver removed at liver transplantation. A, Prominent fibrotic septum separating HCC (left) and cirrhotic liver (right). B, Cellular detail of HCC showing enlarged hepatocytes in a trabecular pattern, pleomorphic nuclei, prominent nucleoli, and swollen cytoplasm due to bilirubinostasis.
of this patient, we conclude that a new hepatic lesion during adequate NTBC
treatment should be considered highly
susicious for HCC even when imaging
techniques do not show a profile
characteristic of HCC and there are no
clear increases in AFP levels.
Moreover, the additional value of other
parameters for early detection of HCC
in HTI should be investigated.
Baumann et al\textsuperscript{17} reported promising
results with lens culinaris agglutinin-A
for HT1, but other markers such as
des-\textgamma-carboxy (abnormal)
prothrombin, glypican-3, and
squamous cell carcinoma antigen-I
require further investigation.\textsuperscript{8,9,18}

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