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CASE REPORT

Hepatocellular carcinoma in a non-cirrhotic patient with Wilson's disease

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Abstract

We report the exceptional case of hepatocellular carcinoma in a non-cirrhotic patient, whose Wilson's disease was diagnosed at the unusual age of 58 years. The liver histology revealed macrovesicular steatosis with fibrosis, but no cirrhosis. The disease was treated with D-penicillamine for 3 years until acute discomfort in the right upper quadrant led to detection of multifocal hepatocellular carcinoma, which was successfully resected. The histological examination confirmed the malignant nature of the 4 lesions, which were classified according to Edmondson and Steiner as poorly differentiated hepatocellular carcinoma grade 3. The non-tumoral parenchyma showed 80% steatosis with ballooned cells, lobular inflammation, septal fibrosis but no cirrhosis. Hepatocellular carcinoma is rare in Wilson's disease, especially in the absence of cirrhosis. The literature's 28 published cases are reviewed and the contributory role of copper in the hepatocarcinogenic process is discussed.

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Key words: Wilson's disease; Hepatocellular carcinoma; Hepatocarcinogenesis; Copper; Liver; Fibrosis; Cirrhosis

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INTRODUCTION

Wilson's disease is an autosomal recessive disorder of copper metabolism. Wilson's disease has a worldwide prevalence between 1 in 30 000 and 1 in 100 000[1]. The responsible gene *ATP7B* is located on chromosome 13 and encodes a copper transporter. In Wilson's disease, the copper transporter is mutated and its function is impaired[1]. Wilson's disease has hepatic, neurological, psychiatric and ophthalmic manifestations. Hepatic manifestations are characterized histologically by steatohepatitis, which evolves into cirrhosis if left untreated. Because most cases of Wilson's disease are diagnosed and treated early, hepatocellular carcinoma is a rare sequela. We report the unusual case of a Wilson's disease patient diagnosed at an advanced age and who developed hepatocellular carcinoma in a non-cirrhotic liver.

CASE REPORT

The patient underwent cholecystectomy due to symptomatic gallstones at 51 years of age. Liver biopsies showed macrovesicular steatosis. The circulating levels of gamma-glutamyltransferase remained chronically elevated and the ALT levels were at the upper limit of the normal. A computed tomography (CT) scan performed 5 years later revealed the presence of a 3 cm subcapsular lesion in liver segment VI as well as several ⩽ 1 cm lesions. All lesions displayed a discrete enhancement dur-

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Table 1 Synopsis of patients with hepatocellular carcinoma and Wilson's disease

Ref.	Sex	WD-age (yr)	HCC-age (yr)	Cirrhosis	Medical therapy	Invasive therapy	Status
Guan *et al*[2]	Female	23	27	Yes	Penicillamin	Hepatic resection	Alive
Iwadate *et al*[3]	Male	17	23	Yes	Penicillamin, low copper diet	-	Dead
Lowette *et al*[4]	-	-	-	Yes	Penicillamin	Transplant	Alive
Ikegawa *et al*[5]	Male	28	37	Yes	Penicillamin, zinc acetate dehydrate	Radiofrequency ablation	Alive
Kumagi *et al*[6]	Male	26	66	Yes	Penicillamin, transplant	Transcatheter arterial chemoembolisation	Dead
Kumagi *et al*[6]	Male	27	36	Yes	Penicillamin, transplant	-	Dead
Kumagi *et al*[6]	Male	27	46	Yes	Penicillamin	-	Alive
Lygren *et al*[15]	Male	15	16	Yes	-	-	Dead
Girard *et al*[16]	Male	22	41	Yes	Penicillamin	-	Dead
Kamakura *et al*[17]	Male	26	32	Yes	Penicillamin	-	Dead
Terao *et al*[18]	Male	29	40	Yes	Penicillamin, dimercaprol potassium sulfate	-	Dead
Wilkinson *et al*[19]	Male	31	41	Yes	Penicillamin	-	Dead
Buffet *et al*[20]	Male	45	57	Yes	Penicillamin	-	Dead
Imhof *et al*[21]	Male	18	40	-	Penicillamin	Hepatic resection	Alive
Madden *et al*[22]	Male	61	61	Yes	Penicillamin	-	Dead
Polio *et al*[23]	Male	32	33	Yes	Penicillamin, low copper diet	Chemotherapy	Dead
Cheng *et al*[24]	Female	39	72	Yes	Penicillamin, dimercaprol potassium sulfate	-	Dead
Agret *et al*[25]	Male	73	73	Yes	-	-	Dead
Walshe *et al*[26]	Male	8	46	Yes	Penicillamin	Transplant	Alive
Walshe *et al*[26]	Male	11	42	Yes	Penicillamin	-	Dead
Kumagi *et al*[27]	Male	66	66	Yes	-	Transcatheter arterial chemoembolisation	Dead
Ozçay et al[28]	Male	-	13	Yes	Penicillamin	Transplant	Alive
Aydinli *et al*[29]	Male	22	22	Yes	-	Radiofrequency ablation, transplant	Alive
Xu *et al*[30]	Male	29	29	Yes	-	Transcatheter arterial chemoembolisation, transplant	Alive
Reyes *et al*[31]	Male	59	59	Yes	-	-	Dead
Emlakçioglu *et al*[32]	Female	30	50	-	Penicillamin	Transcatheter arterial chemoembolisation	Alive
Ikubo *et al*[33]	Female	28	54	Yes	Penicillamin, pyridoxal-phosphate	Hepatic resection	Alive
Savas et al[34]	Male	6	12	Yes	Penicillamin, low copper diet	Transplant	Alive

WD: Wilson's disease; HCC: Hepatocellular carcinoma diagnosis.

ing the arterial phase without washout during the portal phase. Radiological controls over the next 2 years revealed no evolution of these lesions. The biopsy of the largest lesion showed fibrotic remodelling corresponding to Metavir F3 or a modified Ishak score of 4 without evidence of cirrhosis, a 25% macrovascular steatosis, a moderate chronic hepatic inflammation and an area with small cell dysplasia. A broad clinical examination was negative for neurological and ophthalmic (Kayser-Fleischer-rings) signs of Wilson's disease. However ceruloplasmin levels below the limit of detection (0.1 g/L) and urinary copper excretion was elevated. A genetic test confirmed a frameshift-mutation in exon 14 and 2 missense-mutations in exons 18 and 21 of the *ATP7B* gene. The patient was treated with D-penicillamine and pyridoxal-phosphate. This treatment was well tolerated. An magnetic resonance imaging with hepatocellular specific contrast confirmed the known lesions, which were stable in size and interpreted as regeneration nodules.

The patient worked as a mechanic, never smoked and consumed less than 10 g alcohol per day. His mother had metastatic breast carcinoma and died of a cerebral haemorrhage. His father suffered from an undefined psychiatric condition. His 2 brothers and 1 sister are in good health. He has no children.

At the age of 61 years, the patient presented with acute pain in the right upper quadrant, which was preceded for several weeks by discomfort. Contrast-enhanced CT revealed 4 hepatic lesions showing enhancement during the arterial phase and washout during the portal phase. Two lesions of 3.7 cm and 2.1 cm were in segment Ⅳ, 1 lesion of 3.2 cm was in the segment Ⅴ and the largest lesion of 9.7 cm was in segments Ⅵ and Ⅶ. A curative resection was performed. The histological examination confirmed the malignant nature of the 4 lesions, which were classified according to Edmondson and Steiner as poorly differentiated hepatocellular carcinoma grade 3. The non-tumoral parenchyma showed 80% steatosis with ballooned cells, lobular inflammation, septal fibrosis but no cirrhosis. Moreover, there was a mild iron hepatocellular accumulation (Rowe 1), which was absent on the previous biopsy.

DISCUSSION

All the published cases of hepatocellular carcinoma occurring in patients with Wilson's disease are listed in Table 1. As expected for hepatocellular carcinoma, males predominate whereas female constitute a lower than expected percentage (14%) of this group. Females constitute 30% of overall hepatocellular carcinoma cases. The reason may be that cirrhosis initiated by Wilson's disease

is less carcinogenic than that linked to other cirrhotic conditions and that male gender provides additional susceptibility to initiate hepatocarcinogenesis. Because it is uncertain from the information in previous reports whether other risk factors had been considered and excluded[2-6], it is not possible to fully assess whether common features could link them to the hepatocarcinogenic process in our male patient with longstanding, untreated Wilson's disease. However, our patient was exceptional in that he was non-cirrhotic, whereas all previous cases of hepatocellular carcinoma in Wilson's disease occurred in cirrhotic livers (Table 1).

Long-Evans cinnamon rats, which have a mutated *ATP7B* gene and are therefore an experimental model for Wilson's disease, develop hepatocellular carcinoma spontaneously. However, these animals accumulate iron in addition to copper, and an iron-deficient iron diet can abrogate the development of liver tumors[7]. This was attributed to the role of iron in promoting reactive oxygen species and DNA strand breaks[8]. Copper can assume a similar role. Mice receiving copper develop hepatocellular carcinoma, preventable by the concurrent administration of thiamine, which reduces the production of reactive oxygen species in the mitochondria[9]. In addition, copper stabilizes hypoxia-inducible factor-1α (HIF-1α)[10-12] by restraining the activity of the HIF-1α-inhibition factor[10], thereby ensuring the formation of the HIF-1α transcriptional complex[11,12] and the expression of target genes important for angiogenesis, such as vascular endothelial growth factor (VEGF)[10]. Indeed, Martin showed that copper increases VEGF in human hepatoma cells[12]. Another potential carcinogenic property of copper is its ability to stimulate fibroblast growth factor-2[13]. Treatment with D-penicillamine promotes hepatocellular iron accumulation[14]. It is possible that the D-penicillamine treatment of our patient contributed to the oxidative stress through and increase in iron.

When our case is combined with the 28 published cases of hepatocellular carcinoma (Table 1), the mean age at diagnosis of Wilson's disease was 31 ± 18 years: 30 ± 7 years for women and 32 ± 19 years for men. The diagnosis of this genetic disease at such an advanced age suggests that longstanding, untreated Wilson's disease may represent a risk factor for hepatocellular carcinoma. This notion is supported by the observation that the mean age at diagnosis of hepatocellular carcinoma was younger than that observed in patients with other underlying liver diseases (43 ± 18 years).

In conclusion, this case report illustrates that hepatocellular carcinoma does occur in patients with Wilson's disease and that those with longstanding, untreated disease may be particularly vulnerable. Therefore, the importance of determining the fibrosis stage of Wilson's disease patients and of enrolling them in a surveillance program when cirrhotic can only be emphasized.

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