

Hepatocellular Carcinoma in Wilson Disease–related Liver Cirrhosis

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Wilson disease (WD), an inborn copper metabolism defect, is traditionally diagnosed on the basis of clinical features, positive family history, biochemical parameters, the presence of Kayser-Fleischer rings on slit lamp eye examination, and neurologic abnormalities.^{1,2} Occasionally, however, patients may only have hepatic manifestations that mimic nearly any other hepatopathy. Some of these patients may have normal laboratory results such as normal serum ceruloplasmin levels and urine copper excretion, or they may display normal neurologic function. In this subset of patients, the diagnosis of WD becomes complicated and subsequent management difficult. Another interesting facet of WD is the predisposition to hepatocellular carcinoma (HCC), which is a rare but fatal complication in the absence of early diagnosis and initiation of treatment.³ To date, 23 cases of HCC associated with WD have been reported in the literature.³⁻¹³ This case study briefly reviews the pertinent literature¹⁻¹³ and adds another atypical case of WD, which was initially recognized as HCC on fine-needle aspiration cytology and subsequently confirmed by strong family history, the presence of cirrhosis, elevated serum ceruloplasmin levels, increased urinary copper, and significant copper deposition in the liver parenchyma.

Case Report

A 59-year-old white man complained of gradually progressive pedal edema, increasing abdominal girth, and a 15-pound weight gain over a 3-week period. His past medical history included hypertension, diabetes mellitus type II, hyperlipidemia, osteoarthritis, osteomyelitis of the left foot with status post–below-the-knee amputation 15 years ago and cervical myelopathy with status postdiscectomy of the C5 through C6 vertebrae 5 years ago. The patient's medications were aspirin 325 mg QD, atenolol 50 mg QD, ibuprofen 600 mg

TID, NPH 35 U subcutaneous BID, lisinopril 20 mg QD, metformin 850 mg BID, niacin 500 mg QHS, psyllium 1 tsp QD, and beclomethasone (Beconase AQ, GlaxoSmithKline) 1 spray in each nostril QD. He did not have any known drug allergies. The patient lived alone, worked as a contractor, was a social drinker, had a prior history of smoking 10–15 packs a year, and had no history of illicit drug use. His mother died at the age of 90 from a stroke, and his father, a nondrinker, died in his forties from liver cirrhosis.

Abnormal physical findings included deep tan, mild scleral icterus, palpable liver edge 4 cm below the right costal margin, two-plus edema to the level of the knees, and left below-the-knee amputation stump. There was no evidence of ataxia, asterixis, or neurologic abnormalities.

Pertinent laboratory data were normal hemograms and differential counts, electrolytes within reference limits, prothrombin time of 39.4 sec (ref, 22.8–39.8), aspartate aminotransaminase of 203 IU/L (ref, 1–50), alanine aminotransaminase of 177 IU/L (ref, 1–53), alkaline phosphatase of 631 IU/L (ref, 30–110), total bilirubin of 3.8 mg/dL (ref, 0.1–1.2), direct bilirubin of 3.4 mg/dL (ref, 0–0.8), and albumin of 2.1 g/dL (ref, 3.5–5).

Hepatitis panel testing was negative, and other miscellaneous measurements included iron of 112 µg/dL (ref, 35–150), total iron-binding capacity of 331 µg/dL (ref, 250–450), iron saturation of 33.8% (ref, 10–50%), ferritin of 166 ng/mL (ref, 22–322), ceruloplasmin of 223 mg/dL (ref, 20–60), and hemochromatosis genotyping that tested negative for the 282Y and H63D mutations. Autoimmune studies (antinuclear antibody, antimitochondrial, antismooth muscle, and alfa-1-antitrypsin) were also negative. Other findings included polyclonal gammopathy serum on protein electrophoresis, consistent with acute inflammatory pattern, carcinoembryonic antigen of 1.8 ng/mL (ref, 0.5–5), beta-human chorionic gonadotrophin of less than 2.0 mIU/mL (ref, 0–10), alfa-fetoprotein of 3.8 ng/mL (ref, 1.3–8.1), and carbohydrate antigen 19-9 of less than 3 IU/mL (ref, 0–36). Computed tomography (CT) scan of the abdomen

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Figure 1. Computed tomography scan reveals a diffusely enlarged liver of probable cirrhosis without distinct mass lesions.

revealed a diffusely enlarged liver and probable cirrhosis (Figure 1). Subsequent CT scan–guided fine-needle aspiration cytology revealed a well-differentiated trabecular HCC in micronodular cirrhosis (Figure 2).

Further discussion with the patient's family revealed that a niece, at the age of 20, was transplanted for fulminant hepatic failure secondary to WD. Slit lamp examination was negative for Kayser-Fleischer rings, and serum copper levels measured 0.25 $\mu\text{g}/\text{mL}$ (ref, 0.75–1.45), whereas urinary copper measured 117 $\mu\text{g}/24$ hours (ref, 15–60).

The patient was immediately treated with symptomatic regimens. Two hospital readmissions within 2-week intervals were highlighted by watery diarrhea, pruritus, right upper quadrant abdominal pain, increasing jaundice, alcoholic stools, and dark urine. Ascitic fluid analysis was transudative and negative for malignancy. The hospital stay was also characterized by gradual deterioration. The patient became terminal and developed hypotension, shock, acute renal failure, hyperkalemia, and metabolic acidosis. Intravenous hydration, pressors, and antibiotics had no discernable effects.

Autopsy confirmed the diagnosis of a well-differentiated HCC in WD-related liver cirrhosis with metastases in both lungs (Figure 3). The liver copper stain was positive, and the liver copper load was greater than 1,000 $\mu\text{g}/\text{g}$ (ref, 10–35). Brain imaging revealed hepatic encephalopathy with negative copper stain/deposition and no lenticular nucleus degeneration.

Discussion

WD is an autosomal recessive metabolic disorder with an incidence of 1:40,000. The WD gene is located on

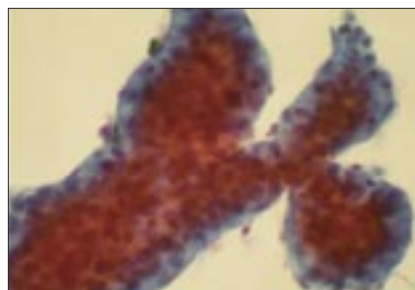


Figure 2. Fine-needle aspiration cytology displays characteristic trabecular growth pattern of malignant hepatocytes associated with occasional benign surface endothelial cells (Papanicolaou stain, 400 \times).

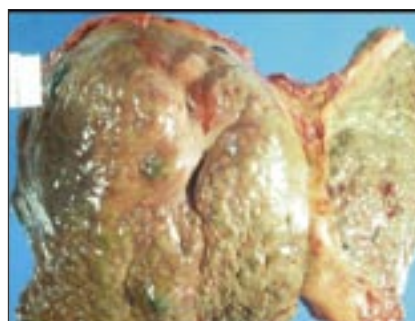


Figure 3. Postmortem evaluation confirmed the diagnosis of well-differentiated hepatocellular carcinoma arising in Wilson disease–related cirrhosis.

chromosome 13 and codes for a copper-transporting P-type ATPase-ATP7B. Mutations of the WD gene cause impaired biliary copper excretion, resulting in copper accumulation in many vital areas, including the liver, central nervous system, and cornea. Patients may therefore develop cirrhosis, neurologic manifestations, and Kayser-Fleischer rings.¹⁻¹³

Although hepatitis and cirrhosis are well-recognized complications of WD, HCC is extremely rare as a complication. The first case of HCC associated with WD was reported in 1959. To date, there have been 23 such cases reported in the literature.³⁻¹³ The patients were almost exclusively male and ranged from 12 to 66 years of age (mean age, 39 years). The average disease duration was 18 years, and the majority of cases received treatment with D-penicillamine chelation. The diagnosis of HCC was confirmed in 12 patients at autopsy, in 3 patients during liver transplantation, and, in 1 case each, via liver core-

needle biopsy, exploratory surgery, surgical lung biopsy for metastasis, and liver fine-needle aspiration cytology. In 4 cases, the diagnosis remained undisclosed.

The diagnosis of WD in our patient was based upon positive family history, presence of cirrhosis, increased serum ceruloplasmin levels, increased urinary copper, and abundant copper deposition in the liver. Etiologies that are more common for HCC and liver cirrhosis, such as hepatitis B virus, hepatitis C virus, alcohol abuse, hemochromatosis, and chronic *Aspergillus flavus* exposure, were excluded clinically, biochemically, and genetically. Among the 23 prior cases in the literature, our index case is one of the oldest patients with HCC and WD and the second to be initially recognized as HCC.³⁻¹³ This atypical presentation of WD occurs in 10–14% of patients and is largely attributed to the diversity of WD gene mutations and phenotypes.³

Carcinogenesis in WD is thought to be the result of accumulated copper in the liver and underlying cirrhosis. Although copper accumulation was originally thought to have a potential protective effect against hepatocarcinogenesis, recent evidence suggests otherwise. Copper deposition in the liver is actually a risk factor for the development of HCC. Some researchers have also observed that decreased copper in patients following D-penicillamine and other chelator treatments may enhance the risk of developing HCC. A consensus on this topic, however, has yet to be developed.¹⁻¹²

The treatment of WD-related HCC does not differ from HCCs of other etiologies and consists of either surgery or chemoembolization, with variable results. Several cases managed with chemoembolization have resulted in early death because of fulminant liver failure. This unfavorable outcome can be explained on the basis of overwhelming hepatocytic degeneration induced by excessive copper deposits and the effect of anticancer treatment. Liver transplantation is a promising alternative and has also been advocated for patients with end-stage WD. Liver transplantation may not only restore liver function but may also alleviate other clinical symptoms and neurologic dysfunctions of WD.³

As a preventive measure in WD-related HCC, it is important to make an early diagnosis of WD to arrest further progression of hepatitis and cirrhosis. All patients with unresolving abnormal liver function tests should be screened for the possibility of HCC.³

Summary

A 59-year-old white man with atypical presentations of WD was initially diagnosed with HCC. Subsequent follow-up evaluations supported the diagnosis of WD with a strong family history, elevated serum ceruloplasmin levels, increased urinary copper, and significant copper deposition in the liver. The development of HCC in WD is most likely secondary to excessive copper deposition in the liver and concurrent cirrhosis.

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Review

Wilson Disease and Hepatocellular Carcinoma

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Until recently, the association between Wilson disease (WD) and hepatocellular carcinoma (HCC) has been controversial. Early study showed that the incidence of HCC in patients with WD was not statistically higher than that in the general population.¹ Based on animal studies and observed rare events of HCC that developed in patients with WD, it was thought that excessive copper might have a protective effect on hepatocarcinogenesis.²⁻⁴ However, newly emerging clinical and experimental data indicate that WD is a risk factor for HCC.^{2,4-22}

WD is a rare autosomal recessive metabolic disorder with an incidence of 1:40,000.²³ To date, more than 20 cases of HCC have been reported in the setting of WD.^{2,4-22} Nearly all these cases were identified in relatively young patients (mean age, 40 years) with classical presentations of WD: hepatic, neurologic, or ophthalmologic manifestations, or combinations of these manifestations. The vast majority of classic WD cases (80%) were diagnosed during the first decade of life, and the patients were treated with chelating agents or died early in life before the development of HCC, which requires an average of 18 years.^{1,2,4-22} As a result, the previously low incidence of HCC that was observed in this group of young patients with classical WD may be biased.

It is well known that there is a high variability in clinical and pathologic presentations of WD, most likely related to the heterogeneity of the genetic abnormalities.^{1,23-25} More than 300 distinct mutations have been identified since the gene for WD was first reported in 1993. The implicated gene encodes a transporting P-type ATPase (ATP7B).^{1,23,26} Specific mutations may affect individual processes of copper sensing, copper-mediated trafficking, and copper transport, contributing to the diverse clinical manifestations of WD.²⁷ Mutations associated with severe impairment of copper metabolism result in grave liver disease early

in life. Minor mutations may explain late onset of the disease (at 50–60 years of age), atypical clinical presentation (only hepatic or neurologic manifestations), and slow progression of the disease. These atypical cases of WD have been reported in approximately 10–15% of patients,^{1,15} and some researchers have postulated that at least 50% of patients may have either atypical presentations or remain undetected for life. These patients may have normal ceruloplasmin levels, normal copper urine excretion, and normal liver function tests. Even in patients with symptomatic liver disease, liver biopsies may produce deceptively low yields for the diagnosis of WD, as histologic abnormalities may be nonspecific or may mimic other hepatic disorders such as acute hepatitis or chronic active hepatitis with or without cirrhosis.^{1,18,24} Hence, atypical cases of hepatic WD may be arbitrarily classified as cryptogenic hepatitis/cirrhosis, unless a clinician diligently examines them for the possibility of WD. Patients with atypical WD are the ones diagnosed and treated with chelating agents later in life, and some patients may never be treated. As a result, they are prone to neoplastic transformation resulting from persistent direct or indirect liver injury.^{1,5,24} The case described by Dr. Reyes²⁸ and a previously reported case are two significant examples of HCC developed under such circumstances. In the case reported by Dr. Reyes, HCC was detected by fine-needle aspiration biopsy in a 59-year-old man who had never been suspected of WD. Subsequent examinations supported the diagnosis of WD based on strong family history, histologic findings, and laboratory results. In a previously reported case of a 29-year-old man who underwent liver transplantation for cryptogenic cirrhosis, the diagnosis of WD was considered only after careful histologic examination and confirmatory quantitative liver copper analysis.⁵ Therefore, the incidence of HCC in patients with atypical WD is underestimated.

The hypothetical protective effect of copper that was postulated in early reports has recently been refuted by several animal and in vitro studies. In the Long-Evans-Cinnamon rat model of human WD, a long and persistently elevated hepatic copper level resulted in the development of HCC in aged animals.²⁹ Copper chelation at an early disease stage in these animal models showed that neoplastic transformation of the liver could be prevented by timely treatment.^{30,31} These findings suggested that copper overload is a risk factor for HCC and that chelation of copper may reduce the incidence of HCC associated with WD. The results may also explain the rarity of HCC occurring in patients with typical WD who receive early chelation therapy.

On the other hand, clinical and experimental evidence does not necessarily indicate a causative relationship

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between copper overload and HCC. The mechanism of tumorigenesis in hepatic WD is complicated and may be multifactorial.^{10,11,13} Copper overload plays a critical role in the initial liver injury that eventually leads to chronic inflammation and cirrhosis; however, its direct oncogenic potential requires further investigation. It is believed that cirrhosis as a continuous process of degeneration-regeneration leads to neoplastic transformation in hepatic WD via a mechanism of tumorigenesis similar to that of other etiologies (eg, viral, alcoholism).^{5,11,32} Supportive evidence comes from the fact that virtually all reported cases of HCC associated with WD developed in the setting of well-established cirrhosis.^{2,4-22}

Prevention of HCC in patients with WD relies on early diagnosis and early intervention to avoid persistent liver damage. For those patients with cryptogenic cirrhosis and HCC, atypical WD should be included as a differential diagnosis.^{1,32} The treatment of HCC associated with WD is no different from HCC treatment associated with other etiologies; resection, transplantation, and chemoembolization are among the treatments of choice.^{5,7,8,25,33,34}

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