An Extremely Rare Case of Wilson's Disease Related Cirrhosis in a Patient with Neurofibromatosis Requiring Liver Transplant

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Introduction

Wilson's Disease (WD), also known as hepatolenticular degeneration, is a rare cause of end stage liver disease with a prevalence of approximately one case in 30,000 live births in most populations[1]. Similarly, neurofibromatosis type 1 (NF1) is a rare neurocutaneous disorder with an incidence of approximately 1:2600 to 1:3000 individuals[2]. We present an extremely rare case of Wilson's disease in a patient with neurofibromatosis requiring liver transplant.

Clinical Presentation

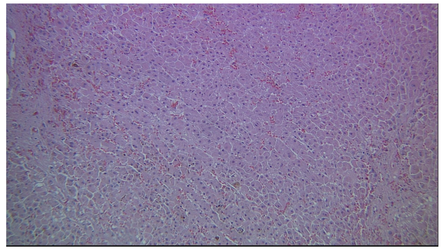
A 34-year-old man presented to the emergency department for bilateral lower extremity swelling. He also reported fatigue and jaundice for one month. His past medical history was significant for NF1 and a previous history of abnormal liver enzymes. Upon presentation, his physical exam was significant for jaundice, scleral icterus, and pitting edema on bilateral lower extremities. His blood work showed Total Bilirubin 15.5 mg/dL, Alkaline Phosphatase 228 U/L, ALT 575 U/L, AST 297 U/L, Prothrombin Time 27.2 sec, INR 2.66, Sodium 138 mmol/L, Platelet 110 10*3/uL, Albumin 2.0 g/dL; his MELD-Na score was 27. An MRCP was done and negative for choledocholithiasis. He was treated with N-Acetyl Cysteine infusion and transferred to our institution for evaluation for liver transplantation.

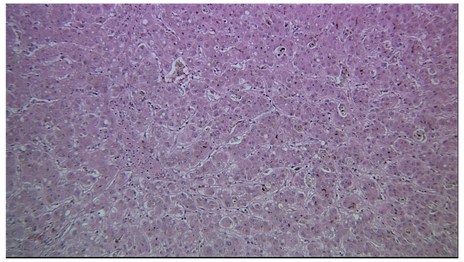
Additional workup was subsequently performed and significant for Ceruloplasmin 10 mg/dl (low), 24-hour Urine Copper 782 ug/24 hours (high), Ferritin 2,000 ng/ml, AFP 38 ng/ml, CEA 8.3 ng/ml, IgG 2457 mg/dl, Alpha-1-Antitrypsin 197 mg/dL (normal 95-164 mg/dL). Hemochromatosis gene testing was negative (C282Y, H63D, S65C). Serologies for autoimmune conditions, including anti-smooth muscle antibody and antimitochondrial antibody were negative. Serologies for HBV, HCV, HAV, CMV, HSV, EBV, HIV, and VZV were negative for acute infection.

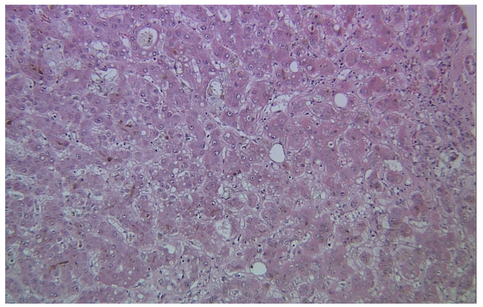
Clinical Presentation (continued)

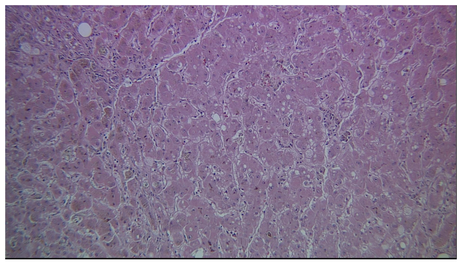
A trans-jugular liver biopsy was performed, the portal gradient was 14 mmHg, and histology showed severe cholestatic hepatitis, evolving cirrhosis (Stage 3-4), increased iron deposition, and mild interface activity. Kayser–Fleischer rings were not seen on slit lamp exam. His clinical course was complicated by ascites requiring paracentesis.

Liver transplant evaluation was completed, and the patient received an orthotopic liver transplant. A liver biopsy at that time was significant for elevated copper concentration of 1906 mcg/g dry weight (reference value: <50 mcg/gram) in the liver tissue, strongly suggestive of Wilson's disease. Histology revealed minimally active cirrhosis and severe intracanalicular and intracytoplasmic cholestasis. Wilson's disease genetic sequencing demonstrated one pathogenic variant (c.2731-2A>G; Heterozygous) and one variant of uncertain significance (c.1171T>C; Heterozygous) in the ATP7B gene.









Figures 1-4. Photomicrographs of liver biopsy with H&E stain showing changes of cirrhosis

Discussion

Wilson's Disease (WD) is a genetic disorder of copper metabolism causing impaired biliary copper excretion and leading to accumulation of copper in several organs, most notably the liver, and eventually leading to cirrhosis. The brain can also be affected, causing neurological and psychiatric manifestations[3].

WD results from an autosomal recessive mutation in hepatocyte copper-transporting ATPase (ATP7B gene; chromosome 13), which leads to decreased copper incorporation into apoceruloplasmin and excretion into bile, leading to decreased serum ceruloplasmin. Copper accumulates, especially in the liver, brain, cornea, and kidneys[4].

Discussion (continued)

Neurofibromatosis type 1 (NF1), previously known as von Recklinghausen disease, is the most common type of neurofibromatosis. The hallmarks of NF1 are the multiple café-au-lait macules and associated cutaneous neurofibromas. Other possible manifestations include optic gliomas, Lisch nodules (pigmented iris hamartomas), pheochromocytomas, focal neurologic signs (often from meningiomas), and bone lesions[5].

NF1 results from mutations in NF1 tumor suppressor gene on chromosome 17 (encodes neurofibromin, a negative RAS regulator). It is autosomal dominant with 100% penetrance rate but with variable expressivity, meaning that patients with the same genotype have varying phenotypes and disease severity[6].

WD and NF result from two uniquely different mutations on different chromosomes with different inheritance patterns. In our patient, it remains a mystery if those two diseases occurred as a result of extremely rare odds of inheritance or as a result from a non-familial incident leading to both mutations sporadically.

References

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