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Hepatocellular Carcinoma due to Hemochromatosis in a Young Patient- A Diagnosis Dilemma

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ABSTRACT

Hemochromatosis causes excess iron deposits in multiple organs, leading to various clinical manifestations. C282Y and H63D are the most common mutation. Diagnosing hemochromatosis is based on clinical characteristics, biochemical abnormalities, radiological findings, and genetic testing with liver biopsy. The literature review also showed 13 cases of developed HCC without cirrhosis in hemochromatosis patients. The increased risk of HCC is associated with excess iron deposition that promotes oxidative DNA damage and increases free radical activity. The amount and duration of iron overload are directly proportional to the risk of development of cirrhosis and HCC.

Keywords: Hepatocellular carcinoma; Hemochromatosis; H63D; C282Y; Liver cancer

INTRODUCTION

Hemochromatosis is a condition characterized by excess iron deposits causing multiorgan dysfunction due to the body's failure to eliminate it. Hereditary hemochromatosis has a prevalence of 1 in 200 to 300 individuals and is the most prevalent autosomal recessive condition in whites.[1] Men are affected 2-3 times more than women, with an estimated ratio of 1.8:1 to 3:1.[2] The most mutations are C282Y and H63D. The most implicated C282Y is a missense mutation at amino acid position 282 with cysteine-to-tyrosine substitution, and the H63D HFE mutation is histidine-to-aspartic acid substitution at amino acid position 63.[3] A study done in the US estimated the prevalence of C282Y and H63D mutation as 5.4% and 13.5% respectively.[4]

The clinical presentation in hemochromatosis varies according to the organ affected, but almost all patients complain of arthralgias, fatigue, and lethargy as early manifestations. However, affected individuals typically remain

asymptomatic until adulthood, and a diagnosis is frequently delayed until several systems are impacted. The liver, pancreas, heart, and other endocrine organs are the most affected organs with late clinical manifestations such as liver cirrhosis, hepatocellular carcinoma, diabetes mellitus, cardiomyopathies, hypopituitarism, arthralgia and chondrocalcinosis, hypogonadism, skin pigmentation.[5]

The initial suspicion of hemochromatosis is frequently based on clinical characteristics, biochemical abnormalities, and genetic testing with liver biopsy in the later phase of diagnosis.[6] Increased serum ferritin levels and transferrin saturation are required for diagnosis. Serum ferritin levels are the most impactful prognostic indicator of disease severity.[5] Approximately six percent of patients with hemochromatosis and cirrhosis progress to hepatocellular carcinoma (HCC).

The case report highlights the malignancy, hepatocellular cancer secondary to hemochromatosis in a young patient who presented with fatigue, elevated liver enzymes, and diabetes mellitus. Further workup for deranged liver enzymes revealed masses in the liver suggestive of malignancy without any specific feature for cirrhosis, which is a clinical manifestation of the disease. This was further supported by the genetic analysis revealing hemochromatosis in our patient.

CASE REPORT

A 27-year-old male with a past medical history of Diabetes, Hypertension, Hyperlipidemia, and Class III Obesity presented to the Emergency Department with fever, non-productive cough, generalized weakness, fatigue, and dizziness. It was associated with abdominal pain, which was dull and poorly localized and later subsided. Despite having a normal appetite, he reported significant weight loss of about 14 lbs and 100 lbs in the last one and six months, respectively. He denied any chest pain, shortness of breath, nausea, pruritis, melena, haematochezia, diarrhea, abdominal distension, dysuria, and swelling of the lower extremities. His current medication includes metformin, rosuvastatin, and prazosin. He consumes alcohol but does not smoke cigarettes nor uses smokeless tobacco, illicit drugs, herbal tea, or medication.

The patient was alert, oriented, and not in acute distress, with a BMI of 47.5 (Grade II obesity). His vitals were within normal limits. On examination, yellowish discoloration of sclera and skin along with brown discoloration of the skin over the bilateral shin were noted, and his abdomen was soft and non-tender with normal bowel sound. His respiratory, cardiac, and neurological findings were unremarkable.

The laboratory findings revealed hemoglobin 10.6 gm/dl, TLC 13.84, Platelets 369 k/UL, RDW 20.3 %, MCH 24.6 pg, MCV 81fl, INR 1.28, CRP 12.68, Sodium 133 mg/dl, Potassium 3.9mg/dl, Calcium 9.2 mg/dl, BUN 6 mg/dl, Creatinine 0.5 mg/dl**,** lactate 3.7mmol/L, lipase 13U/L, ammonia 38 Umol/L, GGT 296 and 130 U/L. His liver function is listed below (Table 1), and iron profile studies (Table 2).

Table 1: Liver Function Test Results

	Day1	Day2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Glucose (mg/dl)	95	91	103	79	100	95	92	86	82
AST (U/L)	113	94	144	108	102	112	113	114	121
ALT (U/L)	241	211	40	29	28	32	32	35	34
ALP (U/L)	149	162	277	213	212	263	306	343	387
ALBUMIN	4	4	3	2.8	2.8	3	3	3	2.9
Total Bilirubin (mg/dl)	6.9	7.7	3.2		2.4	1.9	1.9	1.7	1.8
Direct Bilirubin (mg/dl)			1.9						
Creatinine (mg/dl)	1.2	1.1	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table 2: Iron profile studies

	Laboratory value	Reference
Serum Iron	25	59-158 ug/dl
Ferritin	1561	30-400 ng/ml
Total Iron Binding Capacity (TIBC)	169	149-505 ug/dl
Percentage saturation	15	20-50%

Similarly, the patient had an elevation of AST, ALT, ALP, and total bilirubin for the past few months, with maximum recorded levels as 144 U/L, 104 U/L, 277 U/L, and 3.2 mg/dl, respectively. He had no history of melena, hematochezia, hematemesis, easy bruising, and hemorrhoids and never had esophagogastroduodenoscopy or colonoscopy.

He has procalcitonin 0.3 ng/ml and NT pro-BNP 294 pg/ml. On further investigation, the viral panel, including Hepatitis B Surface antigen and IgM antibody, Hepatitis A IgM antibody, Hepatitis C antibody, Epstein Barr virus, Cytomegaly virus, and infectious causes like Lyme disease, phagocytophilum, and Babesia were negative. The urine drug screen was also negative. Other components of the investigation are listed below in Table 3.

Table 3: Screening Tests

Component	Value	Normal range
Alpha 1 antitrypsin	269	83-119 mg/dl
Ceruloplasmin	45	18-36 mg/dl
Smooth Muscle Antibody screen	Negative	
Mitochondrial antibody screen	Negative	
CEA	2	<5ng/ml
PSA SCREEN	0.8	<4ng/ml
Ca19-9	<3	<34 U/ml
Beta-HCG quantitative	<1	<1mIU/ml
AFP	1.9	<8.3ng/ml

A contrast CT scan of the abdomen was performed, which showed cirrhotic liver morphology and portal hypertension evident with splenomegaly and ascites. Additionally, numerous hepatic lesions throughout the hepatic parenchyma measuring 2.5-2.8 cm. Furthermore, an MRI scan of the abdomen revealed hepatomegaly with innumerable centrally necrotic rim-enhancing lesions throughout the liver concerning metastatic lesions or possible abscesses (Figure 1). Endoscopy was normal, and colonoscopy showed multiple erosions in the caecum, and biopsy revealed negative for dysplasia and focal active colitis. Thus, the patient was initially treated with piperacillin-tazobactam and was later discharged with ciprofloxacin and metronidazole for probable infectious cause with a plan for liver biopsy and hemochromatosis analysis.

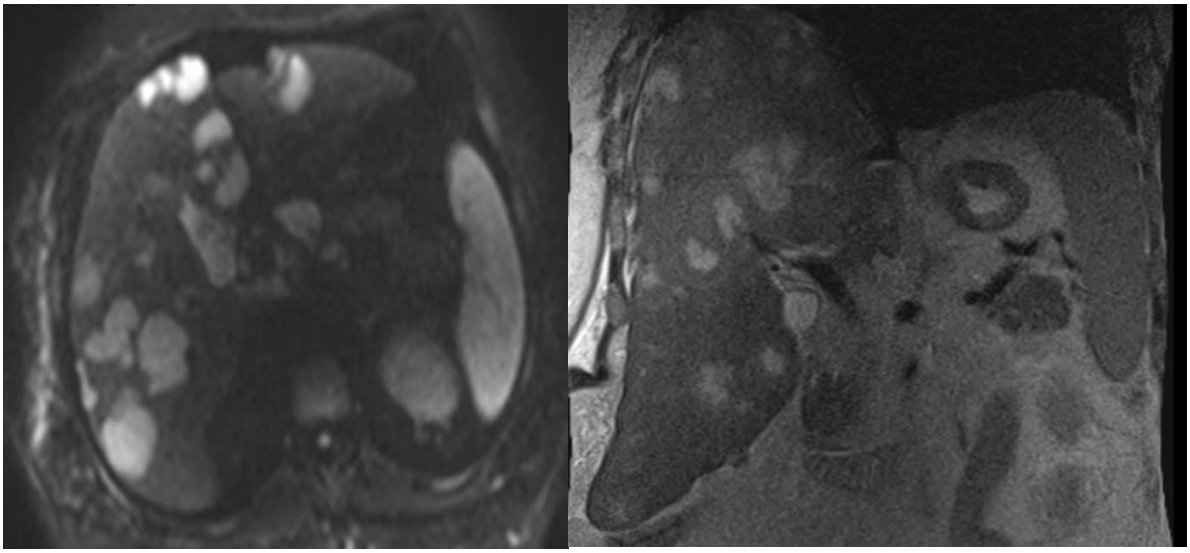

Figure 1: MRI showing multiple masses in the liver

Ultimately, hemochromatosis analysis was positive for the one HFE gene pathogenic variant: H63D (Heterozygote). One copy of the H63D pathogenic variant in the HFE gene was detected but was negative for the C282Y pathogenic variant. Genetic counseling and DNA testing for the at-risk family members were considered but have not been performed yet. The flow cytometry for leukemia and lymphoma were negative, and the light chain free kappa per lambda ratio was 1.81 (0.26-1.65). The biopsy also reported liver parenchyma involved by a high-grade neoplasm along with tumor cells showing significant pleomorphism, APAP ptotic debris, and mitotic figures. The special stain revealed LCA and S100 immunostaining results, which supports the diagnosis. However, Immunohistochemical slides show tumor cells to be negative for HepPar1, arginase 1, glypican-3, AE1:AE3 cytokeratin, CAM 5.2, CK 7, CK20, synaptophysin, chromogranin, CD 117 and CD 30.

DISCUSSION

Hemochromatosis affects various organs in the body, and clinical features are related to the organ involved. However, most patients present with severe fatigue or are usually asymptomatic; thus, a diagnosis cannot be reached. A high level of suspicion, along with a significant family history, is often required for the diagnosis of hemochromatosis.

The liver function test is often deranged with elevated aminotransferase levels, not higher than twice the normal levels.[7] The iron profile test, mainly serum ferritin and transferrin saturation, holds high significance in initial diagnosis as hemochromatosis is linked with inappropriate intestinal iron absorption, leading to iron overload and causing end-organ disease. Meanwhile, the ferritin specificity can be altered with inflammatory conditions, and the transferrin saturation test in erythropoietic hemochromatosis might not be reliable in testing for iron overload. Mechanisms apart from iron burden can cause increased transferrin saturation like hemolysis and cytolysis due to increased plasma iron.[8]

As HFE mutation is prevalent in the US, genetic testing for C282Y and H63D can be obtained in patients with elevated iron indices.[6] 90% of cases could be diagnosed with genetic testing. In addition, radiological imaging, such as Magnetic resonance imaging (MRI), is a non-invasive method to measure the iron content of the liver. FerriScan is an MRI-based technology that provides a reliable measure of liver iron content, but this technology is confined to certain diagnostic imaging departments.[9] In context to our patient, he did not bear any significant clinical manifestation other than deranged liver enzymes initially for the first few months, and further workup for elevated enzymes showed multiple masses in the liver revealed by CT and MRI scan.

Hemochromatosis is often associated with various malignancies, among which hepatocellular carcinoma holds a particular position. Approximately six percent of patients with hemochromatosis and cirrhosis progress to hepatocellular carcinoma (HCC). This signifies an increase in 20-fold lifetime risk over the general population and an annual incidence rate of four percent.[10] The literature review also showed 13 cases of developed HCC without cirrhosis in hemochromatosis patients. These increased risk in HCC may be due to the deposition of excess iron that promotes oxidative DNA damage and increase free radical activity. The amount and duration of iron overload are directly proportional to the risk of development of cirrhosis and HCC. Various hepatotoxic risk factors like concomitant viral hepatitis infection (Hepatitis B virus and Hepatitis C virus), tobacco, and alcohol might promote cancer formation by propagation of cell injury, mutagenesis, and fibrogenesis. A study done in Italy revealed a 150-fold increase in the risk of developing HCC who were Hepatitis B surface antigen positive and were consuming alcohol.[11] Besides the alcohol consumption, our patient had a negative viral hepatitis test. However, alcohol consumed by the patient could synergistically affect the development of HCC in our case. Hemochromatosis patients who drink more than 60 grams of alcohol daily have nine times the likelihood of developing cirrhosis than those who drink less.[12] Alcohol is usually responsible for cirrhosis before the malignant progression, and the patient didn't possess any changes in the architecture of the liver parenchyma, as evident by the radiological findings. The

sensitivity and specificity of the alpha-fetoprotein (AFP) using 5.6 ng/ml as a cut-off have 77% sensitivity and 78% specificity for HCC detection;[13] hence the AFP test for our patient is negative.

Thus, excluding all the possible causes of HCC, after the genetic confirmation of hemochromatosis, it seems to be the most plausible cause for our patient, along with the synergistic effect of alcohol. Therefore, further studies regarding the course development of HCC in hemochromatosis are needed to understand the disease course and complications properly.

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