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ORIGINAL RESEARCH

Acute Portal Vein Thrombosis Predicts Concomitant Diagnosis of Hepatocellular Carcinoma in Cirrhotic Patients

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Abstract

Purpose Portal vein thrombosis (PVT) is a common condition in cirrhotic patients and mostly attributed to portal hypertension. The objective of our study was to examine the association of PVT with hepatocellular carcinoma (HCC) in cirrhotic patients.

Methods A retrospective study was performed to identify cirrhotic patients with thrombosis of the portal system. Clinical and laboratory characteristics were collected and analyzed.

Results Thirty-nine patients were identified. Twenty-four out of 39 patients with PVT did not develop HCC (group A) after follow-up time of 38.5 months from the diagnosis of PVT. Eight patients (20.5%) were diagnosed with HCC within two weeks following diagnosis of PVT (group B). Seven patients (17.9%) were diagnosed with tumor thrombus (group C) at time of PVT diagnosis. The average age was 53.5, 66.5, and 69 years for groups A, B, and C respectively. Most patients (75 and 87.5% for groups B and C respectively) diagnosed with PVT and HCC were males. The most common cause of cirrhosis in groups B and C was chronic hepatitis B virus infection (HBV) in 62.5% and 50% respectively. The most common clinical presentation of PVT in group A was abdominal pain in 55.5% compared to new/worsening ascites in 43% and 37.5% for groups B and C respectively. The platelet count in groups B and C was higher as compared to that in group A (126 and 125 vs. 107 thousand, P = NS).

Conclusion In 38.4% of cases, new diagnosis of PVT was associated with concomitant diagnosis of HCC. Identifiable risk factors were chronic HBV infection and higher platelet count.

Keywords Portal vein thrombosis · Cirrhosis · Hepatocellular carcinoma · HBV infection

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Abbreviations

PVT	Portal vein thrombosis
HCC	Hepatocellular carcinoma
MELD	Model for end-stage liver disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
NASH	Non-alcoholic steatohepatitis
USD	Doppler ultrasonography
CT	Computed tomography
VTE	Venous thromboembolism
ICD	International Statistical Classification of Diseases and Related Health Problems
MRI	Magnetic resonance imaging

Introduction

Portal vein thrombosis (PVT) in cirrhotic patients is a frequently diagnosed entity, with an increased incidence with progression to more advanced stages of cirrhosis. PVT incidence is approximately 1% in patients with compensated disease as compared to 8–25% in liver transplant candidates [1, 2]. The pathogenesis of PVT development in cirrhotic patients is multifactorial and includes slow blood flow velocity that has been identified as a risk factor for PVT [3], hypercoagulability, and vessel wall damage [4]. Additionally, a shift to a procoagulant balance is caused by the increased generation of thrombin as well as endothelial-derived procoagulant factors, such as factor VIII, von Willebrand factor, and hyperhomocysteinemia secondary to vitamin B12 and folate deficiencies [5–7]. Moreover, it has been reported that patients with cirrhosis can have elevated levels of antiphospholipid antibodies, which also predispose to thrombotic events [8]. Cirrhotic patients are also at risk for the classic risk factors for venous thromboembolism (VTE) including hospitalizations, decreased mobility, and higher estrogen levels.

Acute PVT may lead to liver function deterioration and hepatic decompensation, esophageal variceal bleeding, and intestinal ischemia [9]. PVT is often diagnosed incidentally, but in some patients decompensation of chronic liver disease is the first sign of the development of PVT. There have been inconclusive findings regarding risk factors for PVT in cirrhotic patients, but prior studies have reported that male sex, previous endoscopic treatment for portal hypertension, thrombocytopenia, hepatocellular carcinoma, and advanced liver failure are risk factors for PVT [10, 11]. We aimed to investigate the potential predictive value of PVT on either the short-term development or the diagnosis of concomitant hepatocellular carcinoma (HCC) in cirrhotic patients at the time of PVT diagnosis.

Materials and Methods

Study Design

The medical records of cirrhotic patients who were admitted to Hadassah University Medical Center due to acute thrombosis of the portal system between 2006 and 2013 were retrospectively reviewed. The patients were identified through the hospital's computerized medical record database based upon the International Statistical Classification of Diseases and Related Health Problems (ICD) coding system. Inclusion criteria included cirrhotic patients who were diagnosed with acute PVT. Exclusion criteria included patients with radiological signs of chronic PVT and patients with previously diagnosed HCC prior to PVT diagnosis. A total of 78 cases were identified during the study period. Of these, 39 cases were excluded due to the presence of radiological signs of chronic PVT, lack of data, or the presence of HCC prior to the diagnosis of PVT. Final statistical analyses were performed in 39 cases.

Data collected included demographics, underlying cause of cirrhosis, clinical presentation (abdominal pain, new/worsening ascites, upper GI bleeding, and hepatic encephalopathy), model for end-stage liver disease (MELD) score at the time of PVT diagnosis, concomitant diagnosis of HCC at the time of PVT diagnosis, and laboratory characteristics. HCC in our study was diagnosed by the detection of arterial hypervascularity and portal or delayed venous washout as assessed by CT/MRI according to the recent published guidelines from professional societies, the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) [12].

Statistical Analysis

All analysis was performed using Excel 2003 (Microsoft, Redmond WA, USA). The variables were expressed as mean/average. The comparison of two independent groups was performed using Student's *t* test. All tests applied were two-tailed. *P* value of 0.05 or less was statistically significant.

Results

Overall 39 patients were included in the study. Twenty-four out of 39 patients (61.5%) did not develop HCC at an average follow-up time of 38.5 months after PVT diagnosis (group A). Eight patients (20.5%) were diagnosed with HCC at the same time of PVT diagnosis or shortly thereafter, within two weeks (group B). Notably, for two out of the eight patients (25%) in group B, the diagnosis of HCC was missed by US and later confirmed by CT scan. Seven patients (17.9%) were diagnosed with tumor thrombus (group C) at time of PVT

diagnosis. The average age in groups A, B, and C was 53.5, 66.5, and 59 years respectively. The most common cause of cirrhosis in group A was non-alcoholic steatohepatitis (NASH) (29%), while HBV and HCV were responsible for 25% and 17% of cirrhosis causes respectively. The most common underlying cause of cirrhosis in groups B and C was HBV in 62.5% and 57% respectively. Doppler ultrasonography (USD) and CT scan with intravenous contrast material were the two most common modalities used for PVT diagnosis. There were no cases of PVT misdiagnosed by all three imaging modalities. However, in group B, two patients (25%) were diagnosed with HCC by CT scan approximately one week after the initial diagnosis of PVT by USD addressing the possibility of false negative results of HCC diagnosis associated with performing USD. The baseline characteristics are shown in Table 1. The most common clinical presentation prior to PVT diagnosis in group A was abdominal pain in 55.5%. While in groups B and C, new/worsening ascites accounted the for most common clinical presentation and occurred in 37.5% and 43% respectively as compared to abdominal pain that occurred in 25% and 14% in groups B and C respectively. This suggests that new/worsening ascites might be a more suspicious sign for HCC. Platelet count was higher in groups B and C as compared to that in group A (126 and 125 vs. 107 thousand, P = NS). In addition, the mean MELD score was significantly higher in group C (15.8) as compared to that in group B (9.1) reflecting more extensive HCC with deteriorating the liver synthetic function. Laboratory results are shown in Table 2.

Furthermore, in group B, one male patient out of 8 patients (12.5%) underwent successful liver transplantation as he had single HCC lesion of 2.2 cm which fulfills the Milan criteria, while the rest of patients were treated by palliative therapy as they were outside the Milan criteria. In group C, one patient (14.28%) was lost follow-up, while none of the rest of patients were treated with either surgical resection of liver transplantation as they exceeded Milan criteria.

Table 1 Baseline characteristics

Variables	Group A	Group B	Group C
Patients number	24	8	7
Average age (years)	53.5	66.5	69
Male/female (%)	54/46	75/25	87.5/12.5
Cause of cirrhosis (%)			
• HBV	25	62.5	57
• HCV	17	25	25
• NASH	29	25	12.5
• AIH	17	0	0
Diagnosis of PVT (%)			
• US	58.3	37.5	57
• CT	33.3	50	43
• MRI	8.3	12.5	0

Discussion

Portal vein thrombosis is a common complication of end-stage liver disease with a variable prevalence ranging from 1 to 28% depending on diagnostic modality [1, 13]. In patients with non-cirrhotic PVT, the underlying cause is often related to hypercoagulable states. However, in patients with cirrhosis, the presence of portal hypertension that characterized by decreased portal blood flow plays a significant role in the PVT development [14, 15]. Still, in patients with cirrhosis, other contributing factors of PVT need to be examined, including evaluation for potential malignancy. Thus, our study aimed to investigate the association between PVT and HCC diagnosis in cirrhotic patients. We found that 20.5% of cirrhotic patients diagnosed with PVT were diagnosed concomitantly or shortly thereafter (up to two weeks) with HCC, and another 17.9% were diagnosed with tumor thrombus on the initial presentation. Sixty percent of patients did not develop HCC at follow-up.

A previous study suggested that the underlying etiology of cirrhosis may affect the prevalence of PVT with hepatitis B virus-related cirrhosis as the leading etiology of HCC leading to acute PVT [16]. Our study showed similar results, as we found that patients with HBV-related cirrhosis diagnosed with PVT were more likely to have concomitant or subsequent HCC diagnosis as compared to NASH as a cause of cirrhosis. Therefore, careful evaluation for HCC is required in patients with HBV-related cirrhosis once diagnosis of acute PVT is established. Prior studies showed that thrombocytopenia is associated with increasing prevalence of PVT, likely secondary to progression of portal hypertension [17, 18]. Interestingly, our study showed that a higher platelet count might be a warning sign for HCC in cirrhotic patients as this possibly may be secondary to HCC-induced paraneoplastic syndrome.

The presence of ascites and abnormal renal function has been shown to be associated with acute PVT in patients with cirrhosis who are on waiting lists for transplantation [19]. However, in our study, renal function was within normal limits in all groups. In our study, abdominal pain was the most common clinical presentation for PVT, while the presence of new-onset/worsening ascites was the most common clinical presentation in those with PVT and HCC suggesting that we should investigate carefully for the presence of HCC once PVT associated with ascites is encountered.

In our study, there were no cases of PVT misdiagnosis via imaging studies. However, in group B, 2 patients (25%) were diagnosed as having HCC by CT scan approximately one week after the initial diagnosis of PVT by USD. This shows

Table 2 Clinical characteristics and laboratory results

Variables	Group A	Group B	Group C	*P* value
Clinical presentation (%)				
• Abdominal pain	55.5	25	14	
• New/worsening ascites	39	37.5	43	
• Hematemesis	11	0	25	
• Hepatic encephalopathy	5.5	14.3	0	
Laboratory results				
• MELD score	14	9	15	$P = 0.01$ (B vs. C)
• Platelets (10^9/L)	107	126	125	$P =$ NS
• INR	1.6	1.28	1.56	$P > 0.1$
• Hemoglobin (Gram %)	11.5	13.2	10.6	$P = 0.03$ (B vs. C)
• Creatinine (micromole/L)	87	82	85	$P > 0.3$

that there is a possibility of false negative results for HCC diagnosis with USD, suggesting that in new-onset PVT, a CT scan with intravenous contrast material is recommended to further evaluate for the presence of HCC. Furthermore, MRI can be used as well for diagnosing PVT with high accuracy. In our study, MRI was performed in only a few patients (3 cases) due to its unavailability and higher costs than CT and ultrasonography.

The limitations of the study include a small sample size and the retrospective collection of the data. Furthermore, not all variables were available for collection and analysis.

In conclusion, in this preliminary small cohort study, we showed that PVT in cirrhosis was associated with concomitant diagnosis of HCC in 38.4% of patients. Possible risk factors include chronic HBV infection-related cirrhosis and the presence of a higher platelet count. Thus, we recommend performing a CT/MRI scan with intravenous contrast material in any newly diagnosed PVT in cirrhotic patients. Future larger prospective trials are needed in order to confirm our findings and to evaluate the exact impact of PVT on short- and long-term diagnosis of HCC as well as to generate stepwise management and follow-up plans in those patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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