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Current Evaluation for the Frequency of Portal Vein Thrombosis and Its Impact among Egyptian Cirrhotic Patients

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- Portal vein thrombosis (PVT) were reported in 17.8% of our cirrhotic patients.
- Hepatocellular carcinoma was the commonest risk factors of portal vein thrombosis followed by sclerotherapy
- Child C class showed highly statistically significant increase in patients with portal vein thrombosis.
- Doppler examination of patients with PVT revealed, Retrograde flow, distention, increased echogenicity at the site of the thrombus and cavernous transformation

List of abbreviations:
Portal Vein Thrombosis (PVT)
Hepatocellular Carcinoma (HCC)

Abstract

Background: *Development of portal vein thrombosis (PVT) is a significant milestone in the natural history of cirrhosi.*

Aim of the Study: *Evaluation of frequency of portal vein thrombosis in cirrhotic patients, determine the possible associated risk factors and consequence of portal vein thrombosis in cirrhotic patients.*

Patients and Methods: *The present study was conducted on 500 cirrhotic patients. All patients were subjected to routine investigations, upper gastrointestinal endoscopy and abdominal ultrsonography with portal doppler examination.*

Results: *The present study revealed portal vein thrombosis (PVT) in 89 patients with frequency 17.8% of PVT among cirrhotic patients. Hepatocellular carcinoma (HCC) was the commonest risk factors of portal vein thrombosis followed by sclerotherapy. Hepatitis C was present in 88.8% of patients with portal vein thrombosis. Elevated liver enzymes, bilirubin and alpha fetoprotein were significantly increased in patients with PVT in comparison with those without PVT. Child C class showed highly statistically significant increase in patients with portal vein thrombosis. The incidence of portal vein thrombosis in cirrhotic patients*

who underwent splenectomy was 50%. Portal vein and spleenic diameter,were significantly increased in patients with PVT in comparison with those without PVT. Retrograde flow, distention and increased echogenicity at the site of the thrombus in addition to cavernous transformation were significantly observed on Doppler examination of patients with PVT.

Conclusions: *PVT is frequently reported in patients with liver cirrhosis especially those with advanced stages as a part from a complex scenario. HCC and sclerotherapy are the most common risk factors of PVT.*

Key Words: *portal vein, thrombosis, cirrhosis, risk factors, outcome.*

INTRODUCTION

Portal vein thrombosis (PVT) is considered a rare clinical and pathological entity [1],[2]. The first case of PVT was reported in 1868 by Balfour and Stewart, describing a patient presenting splenomegaly, ascites, and variceal dilation [3]. Although in the general population PVT is considered a rare event, its prevalence among cirrhotic patients ranges between 4.4%-15%, and is responsible for about 5%-10% of overall cases of portal hypertension [4]. But its prevalence among patients with hepatocellular carcinoma ranges from 20% to 65% [5],[6].

The elevation of conventional coagulation parameters in patients with liver failure does not protective against thrombotic events. Indeed, a deficiency in the natural anticoagulant system in liver failure may actually contribute to a prothrombotic state [7]. Other factors such as platelet dysfunction, endothelial dysfunction, increased levels of von-willebrand factor, and hemodynamic changes related to portal hypertension, all these factor lead to the net coagulation status of patients with liver disease [8]. Thrombus formation usually begins in the portal vein and sometimes extends to other branches of the portal system such as splenic vein or mesenteric vein. The involved blood vessels can be partially or totally occluded resulting in increased portal venous outflow resistance from narrowing or obstructed blood vessel lumens [4], [1], [9] .

As thrombosis usually occurs gradually giving time for the development of cavernous transformation as a result of periportal collateralization around the occluded portal vein, most patients are asymptomatic and do not seek medical attention [9],[2]. However, obvious signs of portal hypertension such as splenomegaly, ascites, and massive hemorrhage from esophageal and gastric varices could also be found [1], [10]. In the acute setting of moderate to severe thrombus occlusion, abdominal pain may be the striking presentation [2],[9],[10],[11]. So, we aimed to assess frequency of portal vein thrombosis in cirrhotic patients and determine the possible associated risk factors and consequence of portal vein thrombosis in cirrhotic patients.

PATIENTS AND METHODS

This study was carried out in Tropical Medicine Department, Faculty of medicine, Zagazig University, during the period from July 2011 to July 2013. five hundred patients with cirrhosis (311 males and 189 females), their ages ranged from 40 to 80 years old (57.12±56) were enrolled. The diagnosis of liver cirrhosis was established clinically, laboratory and radiology. The severity

of the liver disease was assessed according to the Child-Pugh classification. After exclusion of systemic illness that affect survival e.g(heart failure – renal failure), any coagulation disorders, other than hepatic patients, peripheral vascular disease or medications that affect the vascular bed.

After an informed consent and study revision by institutional review board of Faculty of Medicine, Zagazig University, all the patients with liver cirrhosis were subjected to the following:

- Full history taking and thorough clinical examination.
- Liver function tests including, serum bilirubin (total & direct), ALT, AST, total protein, serum albumin, prothrombin time & INR and serum alkaline phosphatase.
- Kidney function tests including serum creatinine and urea.
- Complete blood picture.
- Viral *markers* : Hepatitis B surface antigen (HBs Ag), Hepatitis B core Ab (HBc Ab) , Hepatitis C virus Ab (HCV Ab) using third generation ELISA test .
- Serum alpha-fetoprotein level: In cases suspecting hepatocellular carcinoma.
- Anti mitochondrial antibody (AMA),anti smoth muscle antibodies (ASMA) ,antinuclear antibodies (ANA) and anti liver kidney microsomal antibodies (LKMA). In cases suspecting autoimmune hepatitis.
- Child-Pugh classification was assessed using parameters of serum bilirubin, serum albumin, prothrombin concentration, hepatic encephalopathy and ascites (Pugh et al., 1973). Child classes; (A): 5-6 point (B): 7-9 point (C): 10-15 points
- Abdominal ultrasonography.
- Upper GIT endoscopy to asses the prese-nce and grading of esophageal varices.
- CT Abdomen: We use this imaging study in cases showed focal lesion(s) in ultrasonography to confirm diagnosis of hepatocellular carcinoma. Also it is useful in evaluating the condition of portal vein.
- Doppler US study

  All patients were examined with GE LOGIQ P3 whole body color Doppler machine with multi-frequency transducer

  Doppler parameters and measurements evaluated:

  - Absences or presence of flow
  - Direction of flow
  - Distension at site of thrombus
  - Echogenicity of the thrombus
  - Color flow within the thrombus
  - Cavernous transformation
  - Waveform

STATISTICAL ANALYSIS

Statistical analysis of patient`s data was done using Ep_i- Info (2004) soft ware computer. Quantitative data were expressed as the mean ± standard deviation (M ±SD) and analyzed by independent "t" test. While, qualitative data were expressed as number and percentage and were analyzed by Chi square (X^2) test.

RESULTS

The present study included 500 patients with cirrhosis (311 males and 189 females), their ages ranged from 40 to 80 years old (57.12±56) and revealed portal vein thrombosis (PVT) in 89 patients with frequency 17.8% of PVT among studied cirrhotic patients.

In 27 patients (30.33%) the thrombosis was present in the main trunk only, 16 patients (17.97%) in right branch only, the least common site is the left branch only in 3 patients (3.37%) while, 43 patients (48.31%) showed mixed sites for the thrombosis mainly the main with the right branch (20 patients, 22.47%) which shows statistically significant differences ($p < 0.001$) (data not shown).. Although, males predominate in cirrhotic patients with portal vein thrombosis there is no statistically significant difference ($p=0.065$) between patients with (M/F=63/26) and without (M/F=248/163) portal vein thrombosis (data not shown). Hepatocellular carcinoma is the commonest risk factors of portal vein thrombosis followed by sclerotherapy (fig, 1). There was no significant difference as regard the etiology of cirrhosis between both groups, however, hepatitis C was present in 88.8% of patients with portal vein thrombosis is followed by 9% due to hepatitis B&C followed by 2.2% due to hepatitis B (table, 1). Clinical presentation, laboratory parameters and ultrasonographic evaluation of portal of the patients is shown in table (1,2). Although, there was no significant difference in Child classes between both groups, Child C class showed highly statistically significant increase in patients with portal vein thrombosis, table (3). Retrograde flow, distention and increased echogenicity at the site of the thrombus in addition to cavernous transformation were significantly observed on Doppler examination of patients with PVT table (4).

Table (1): Etiological and Clinical presentation of patients with and without portal vein thrombosis

Etiological parameter	Without PVT N=411	With PVT N=89	*P*
Viral hepatitis (C)	370(90%)	79(88.8%)	0.72
Viral hepatitis (B)	22(5.4%)	2(2.2%)	0. 28
Viral hepatitis (B&C)	17(4.1%)	8(9%)	0.06
Autoimmune hepatitis	2(0.5%)	0(0%)	1.00
P value	< 0.001	< 0.001	
Clinical parameter			
Ascites			
No	79(19.2%)	15(16.8%)	0.60
Mild	114(27.7%)	18(20.2%)	0.14
Moderate	167(40.6%)	44(49.4)	0.12
Marked	51(12.4%)	12(13.5%)	0.78
O.V			
240(58.39%)	77(86.52%)	317	< 0.001
171(41.60%)	12(13.48%)	183	
Hcc			
+ve	12(2.9%)	78(87.6%)	< 0.001
-ve	399(97.1%)	11(12.4%)	
Sclerotherapy			
+ve	84(20.4%)	42(47.2%)	< 0.001
-ve	327(79.6%)	47(52.8%)	
Splenectomy			
+ve	5(1.2%)	5(5.6%)	0.01
-ve	406(98.8)	84(94.4%)	

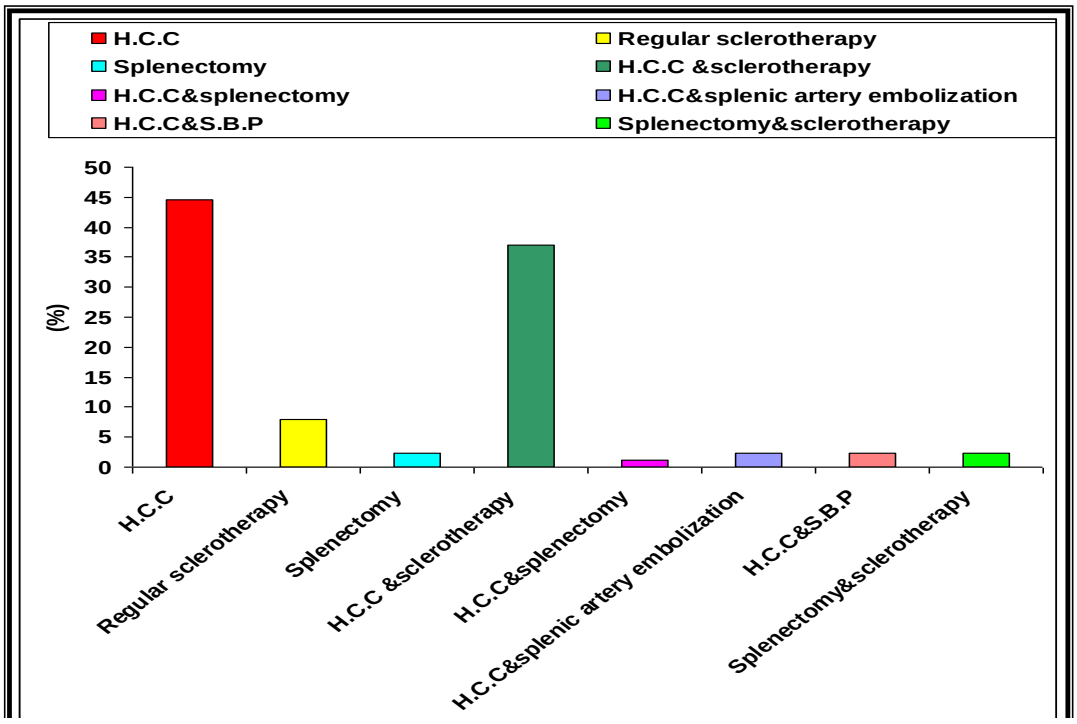


Fig (I): Frequency of risk factors of portal vein thrombosis.

Table (2): Laboratory and Ultrasonographic parameters of patients with and without portal vein thrombosis

Variable		Without PVT N=411	With PVT N=89	*P*
WBC (X103/ml)	> 4 x10/ml	277(67.4%)	52(58.4%)	0.106
	<4 x10/ml	134(32.6%)	37(41.6%)	
Hb(g/dl)	> 12.0 g/dl	44(10.7%)	8(9%)	0.63
	< 12.0 g/dl	367(89.3%)	81(91%)	
Platlet (X103/ml)	>150 X10/ml	17(4.1%)	7(7.9%)	0.136
	< 150 X10/ml	394(95.9%)	82(92.1%)	
ALT (IU/ml)	< 35 IU/L	49(11.9%)	2(2.2%)	0.006
	> 35 IU/L	362(88.1%)	87(97.8%)	
AST (IU/ml)	< 35 IU/L	53(12.9%)	5(5.6%)	0.05
	> 35 IU/L	358(87.1%)	84(94.4%)	
T.protein(g/dl)	> 6 g/dl	220(53.5%)	55(61.8%)	0.15
	< 6 g/dl	191(46.5%)	34(38.2%)	
Albumin (g/dl)	>3.2 g/dl	30(7.3%)	4(4.5%)	0.34
	< 3.2g/dl	381(92.7%)	85(95.5%)	
T.bilirubin (mg/dl)	Up to 1.2 mg/dl	122(29.7%)	4(4.5%)	< 0.001
	> 1.2 mg/dl	289(70.3%)	85(95.5%)	
D.bilirubin(mg/dl)	*Up to* 0.3 mg/dl	72(17.5%)	2(2.2%)	< 0.001
	> .3 mg/dl	339(82.5%)	87(97.8%)	
INR	Up to 1.1	7(1.7%)	1(1.1%)	0.693
	> 1.1	404(98.3%)	88(98.9%)	
Creatinine(mg/dl)	*Up to* 1.4 mg/dl	253(61.5%)	47(52.8%)	0.127
	> 1.4 mg/dl	158(38.6%)	42(47.2%)	
Alphafetoprotein (ng/ml)	< 20 ng/ml	363(88.3%)	31(34.8%)	< 0.001
	> 20 ng/ml	48(11.7%)	58(65.2%)	
Ultrasonographic evaluation of portal and spleenic diameter among studied patients:				
Portal vein diameter	*(mm)*	15.36±1.46	15.74±1.9	0.007
*Spleen diameter**	*(mm)*	15.32±1.65	15.80±1.49	0.013

*=significance significant (p<0.05) highly significant (P<0.001) non significant (p>0.05)

WBC= white blood cells ALT= alanine amino transeferases AST=aspartate amino transeferases T=total D=direct INR=international normalized ratio.

*10 cases had splenectomy 5 cases with portal vein thrombosis (n=84) and 5 cases without portal vein thrombosis (n=406).

Table (3): Child Pugh classification of cirrhosis in patients with and without portal vein thrombosis

Child classification	Without PVT N=411	With PVT N=89	*P*
A	29(7%)	3(3.4%)	0.19
B	138(33.6%)	30(33.7%)	1.00
C	244(59.4%)	56(62.9%)	0.53
Total	411	89	
P	< 0.001	< 0.001	

Significant (p<0.05) highly significant (p<0.001) non significant (p>0.05).

As shown in this table there is no statistically significant differences between Child classes in patients with and without portal vein thrombosis.

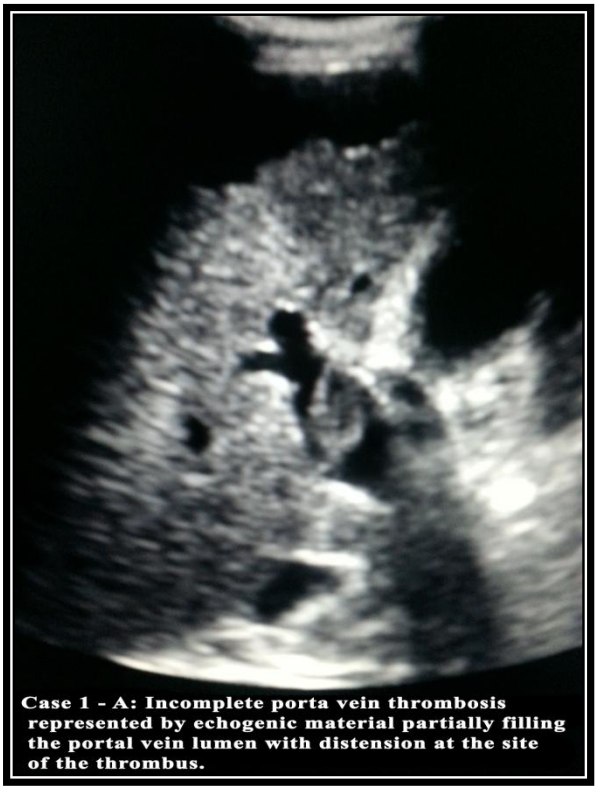
Table (4): Doppler features of cases with portal vein thrombosis.

Variable		Frequency	Percentage	P
Flow	Yes	47	52.80%	0.59
	No	42	47.19%	
Direction of flow*	Antegrade	43	91.48%	< 0.001
	Retrograde	4	8.51%	
Distention at site of thrombus*	Yes	13	14.60%	< 0.001
	No	76	85.39%	
Hepatic mass adjacent to portal vein*	Yes	24	26.96%	< 0.001
	No	65	73.03%	
Echogenicity of thrombus*	Echogenic	87	97.75%	< 0.001
	Hypoechoic	2	2.24%	
Cavernous transformation*	Yes	24	26.96%	< 0.001
	No	65	73.03%	
Colour signal within thrombus*	Yes	28	31.46%	< 0.001
	No	61	68.53%	
Spectral Doppler(pulsatile waves) *	Yes	11	12.35%	< 0.001
	No	78	87.64%	
Velocity*(cm/sec)*		*Mean*	*± SD*	
Before thrombus		11.22	±1.69	< 0.001
After thrombus		4.78	± 1.28	

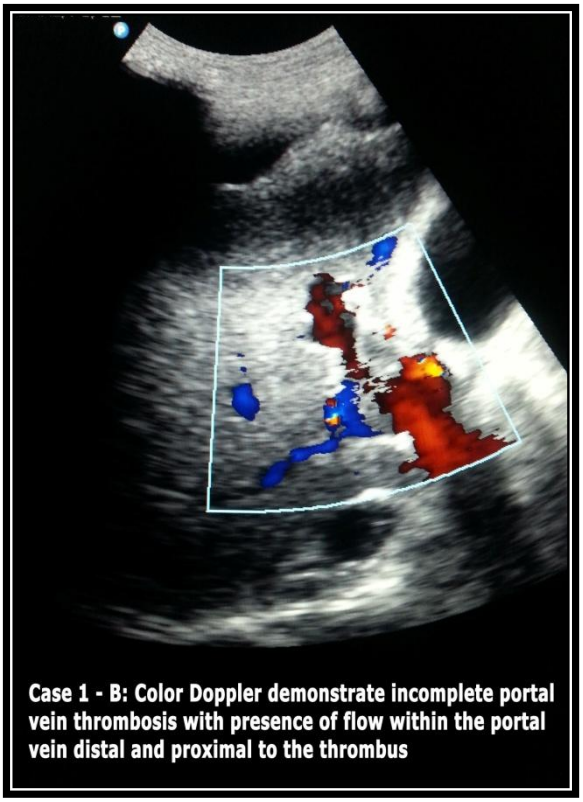
***=Significance Significant (p<0.05) highly significant (p<0.001) non significant (p>0.05).**

This table shows the data obtained by Doppler U/S of portal vein in patients with portal vein thrombosis, there are highly statistically significant differences toward antegrade flow (91.48%), absence distention at site of thrombus (85.39%), no hepatic mass adjacent to portal vein (73.03%), echogenic thrombus (97.64%), no cavernous transformation (73.03%), no color signals within thrombus (68.53%) and no pulsatile waves by spectral Doppler (87.64%), however there is no statistically significant differences as regard presence and absence of flow in patients with portal vein thrombosis.

Case 1:-

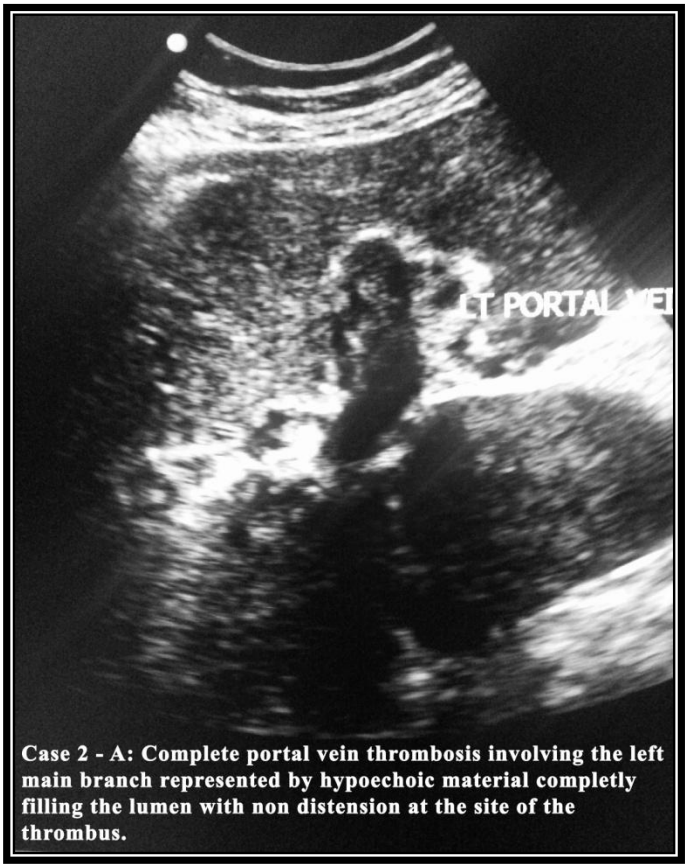


Case 1 - A: Incomplete porta vein thrombosis represented by echogenic material partially filling the portal vein lumen with distension at the site of the thrombus.

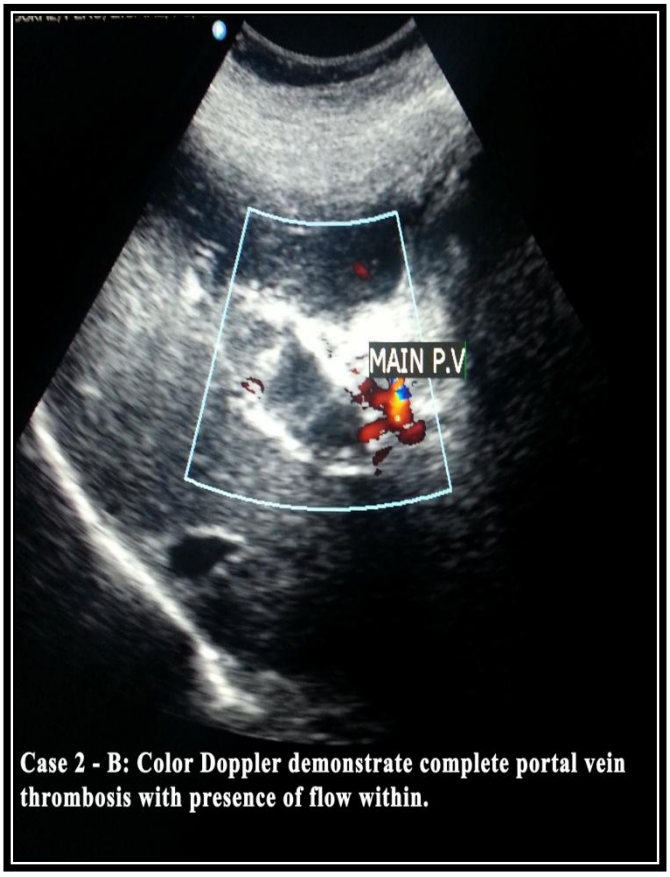


Case 1 - B: Color Doppler demonstrate incomplete portal vein thrombosis with presence of flow within the portal vein distal and proximal to the thrombus

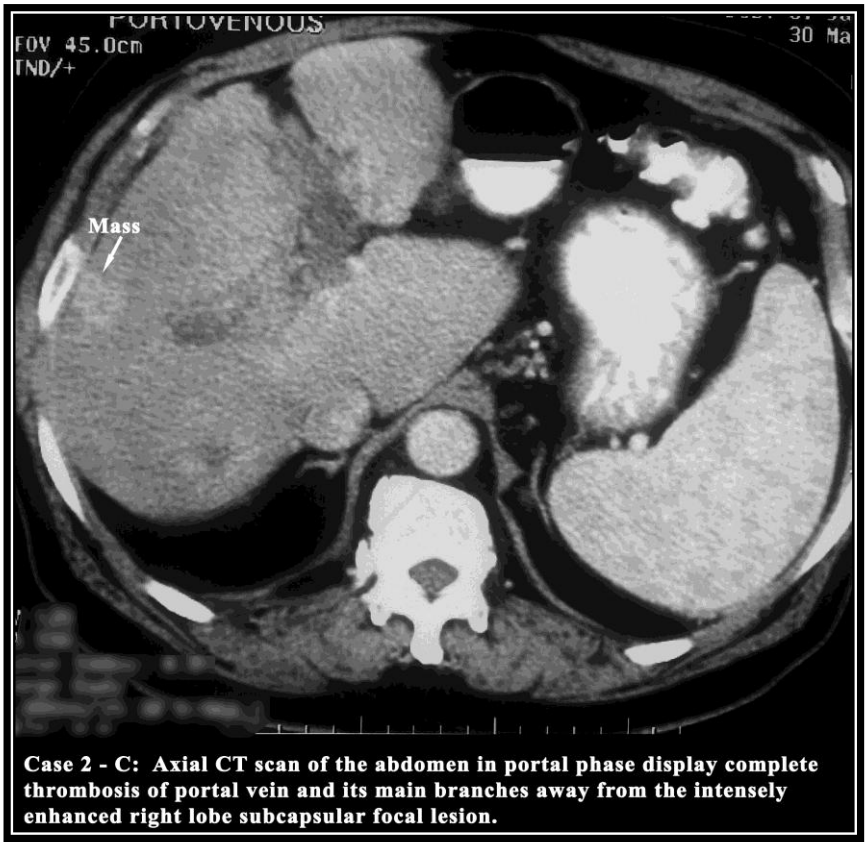
Case 2:-



Case 2 - A: Complete portal vein thrombosis involving the left main branch represented by hypoechoic material completly filling the lumen with non distension at the site of the thrombus.

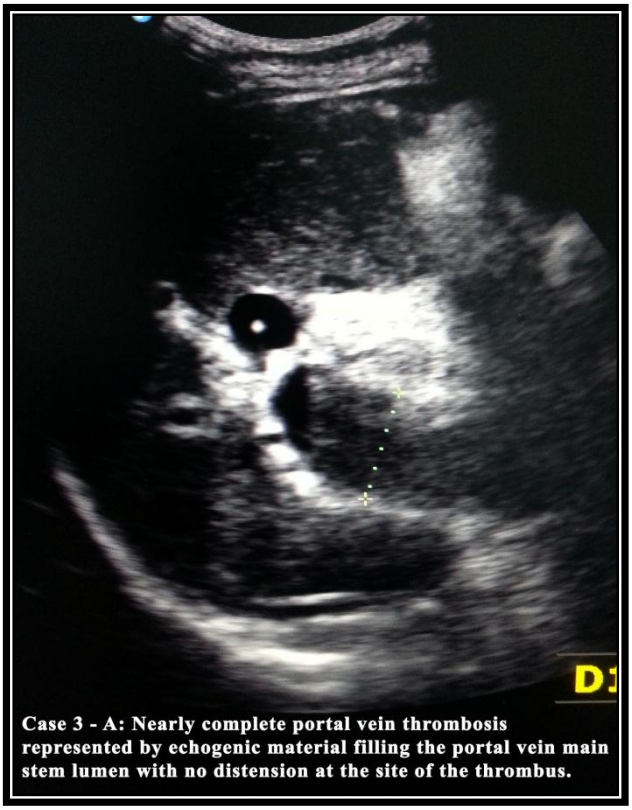


Case 2 - B: Color Doppler demonstrate complete portal vein thrombosis with presence of flow within.

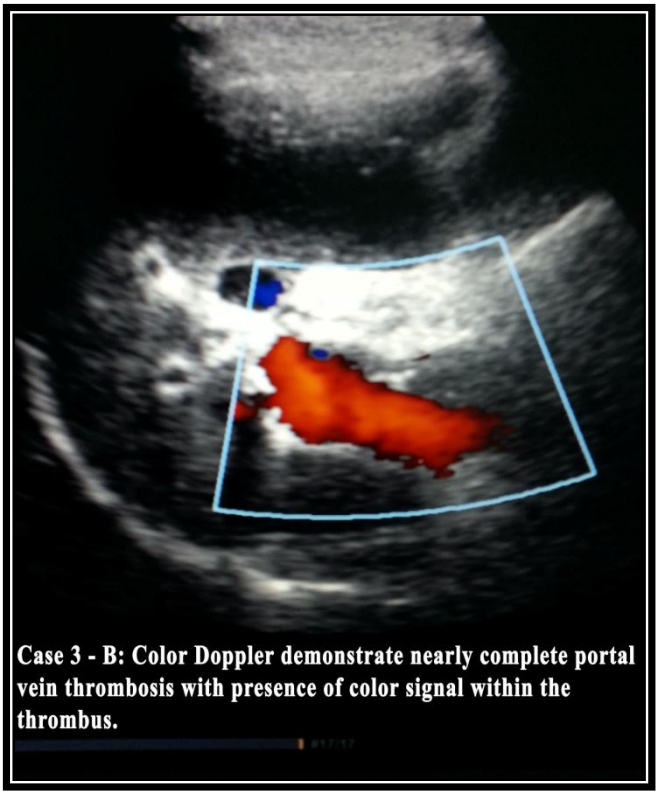


Case 2 - C: Axial CT scan of the abdomen in portal phase display complete thrombosis of portal vein and its main branches away from the intensely enhanced right lobe subcapsular focal lesion.

Case 3:-

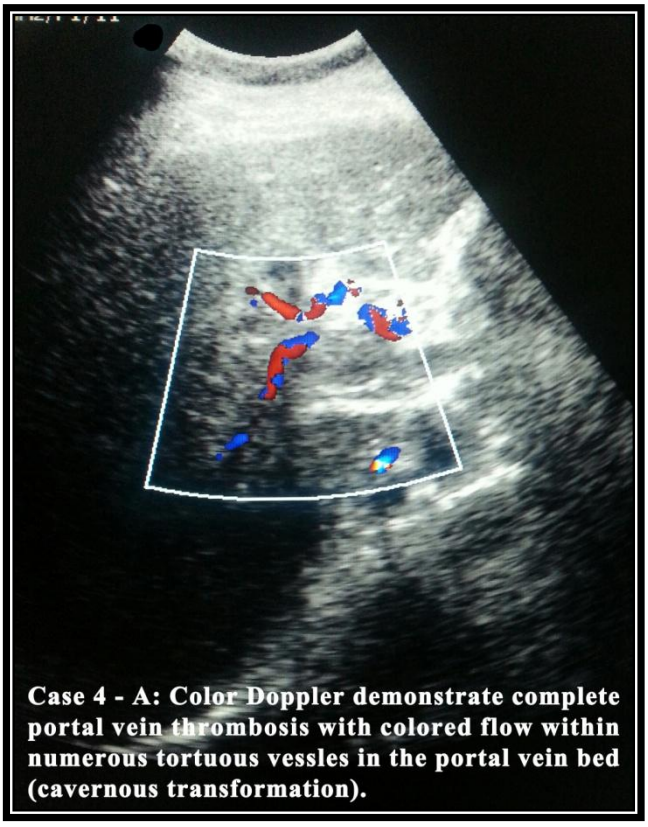


Case 3 - A: Nearly complete portal vein thrombosis represented by echogenic material filling the portal vein main stem lumen with no distension at the site of the thrombus.

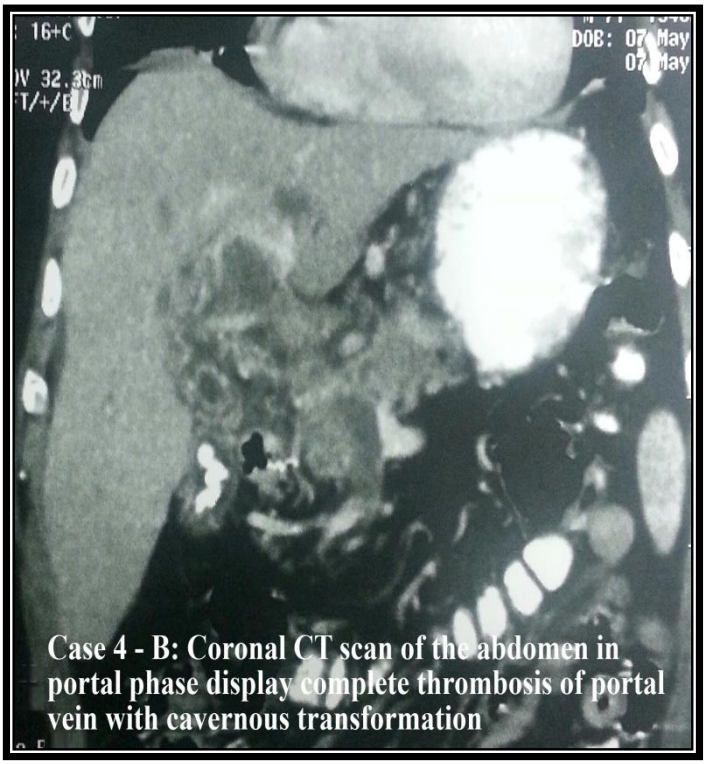


Case 3 - B: Color Doppler demonstrate nearly complete portal vein thrombosis with presence of color signal within the thrombus.

Case 4:-



Case 4 - A: Color Doppler demonstrate complete portal vein thrombosis with colored flow within numerous tortuous vessles in the portal vein bed (cavernous transformation).



Case 4 - B: Coronal CT scan of the abdomen in portal phase display complete thrombosis of portal vein with cavernous transformation

DISCUSSION

Portal vein thrombosis is most often asymptomatic in patients with advanced cirrhosis so that diagnosis is based on systematic imaging. The proper impact of portal vein thrombosis on the natural history of cirrhosis remains unclear. There is no evidence that portal vein thrombosis leads to further deterioration in liver function in advanced cirrhosis [12]. So, we aimed to assess frequency of portal vein thrombosis in cirrhotic patients and determine the possible associated risk factors and consequence of portal vein thrombosis in cirrhotic patients.

In our study the frequency of portal vein thrombosis among cirrhotic patients was 17.8% (89 out of 500 cirrhotic patients).This percentage is closely near to [13] reported that the incidence of portal vein thrombosis in patients with liver cirrhosis was reported to be between 6 and 17%, with a higher incidence in more advanced stages of the liver disease. However, [14] who found that the prevelance was 4.5% only, this difference may be due to that their study is limited to patients who were evaluated for liver transplantation and also be attributed to the difference of regional locality. Other studies showed wide range in the incidence of portal vein thrombosis among liver cirrhotic patients which varied from 0.6% to 64.1% [4], [15], [16], [17]. The variation in incidence of portal vein thrombosis in cirrhotic patients depends on diagnostic methods or the criteria for patient selection. As regard, to the distribution of thrombosis among branches of portal vein we found that the thrombus was found most commonly in the main trunk (78.6%) followed by right branch (57.3%) and left branch (29.2%). These results were in agreement with a previous finding from Italy which revealed that among 701 patients with liver cirrhosis, the thrombus was found most commonly in the main portal trunk [4]. Moreover, a study from China also showed that the right branch was the most commonly affected branch in a series of 108 patients with advanced HCC [18].

In our study the demographic study of cases with portal vein thrombosis showed that the old age males patients predominated than females patients (70.78% vs 29.1%) respectively. This result was similar to those reported by [19] who found that males were 72.9% and females were 27.1% and [14] who reported that males were 61.5% and females were 38.5%. In previous studies of patients with cirrhosis, male sex has shown to be associated with increased risk for developing non tumoral portal vein thrombosis [20],[21],[22]. There was no significant difference as regard the etiology of cirrhosis between both groups, however, hepatitis C was present in 88.8% of patients with portal vein thrombosis is followed by 9% due to hepatitis B&C followed by 2.2% due to hepatitis B. This could be understood as Egypt has the highest prevalence of antibodies to hepatitis C virus (HCV) in the world, estimated nationally at 12.2% of females and 17.4% of males [1].

Several clinical risk factors have been shown to be associated with portal vein thrombosis: they include thrombocytopenia, previous variceal hemorrhage, splenectomy, surgical portosystemic

shunt, and endoscopic treatment of esophageal varices [22],[23].

Trying to search about the possible associated risk factors in cirrhotic patients with portal vein thrombosis, although we did not assess the possible hereditary coagulation defect, it was found that hepatocellular carcinoma is the most common associated risk factor for portal vein thrombosis as it was found in 78 out of 89 patients with portal vein thrombosis (87.6%), However non tumoral portal vein thrombosis was reported in 11 out of 89 patients with portal vein thrombosis (12.4%). Our study was near to the result of [19] who found that H.C.C represented about 81% of cases with portal vein thrombosis but higher than that reported by [24] who stated that hepatocellular carcinoma is the most frequent cause of PVT in cirrhosis, being present in up to 44% of cases.

The current study showed that sclerotherapy which is one of the treatments of esophageal varices has a major risk for portal vein thrombosis as 47.2% of patients with portal vein thrombosis (PVT) were on regular sclerotherapy. Our result was in concordance with that reported by [25] who reported that the data suggest that endoscopic sclerotherapy may incite thrombus formation in portal vein tributaries. and among patients who had undergone prior sclerotherapy, but our result not in agree with that reported by [26] who reported that no patient developed splenic or portal vein thrombosis as shown by arteriography as result to intravariceal and paravariceal sclerotherapy.

In this work, 5 of out 10 cirrhotic patients who underwent splenectomy had portal vein thrombosis. So, the incidence of portal vein thrombosis in cirrhotic patients who underwent splenectomy was 50%. [27] reported that portal vein thrombosis is a recognized complication of splenectomy. This result was not in agree with that reported by [28] who found that the incidence of portal vein thrombosis in cirrhotic patients who underwent splenectomy 1.8%. As regard clinical, laboratory and sonographic profile of the patients, this study, showed that oesophageal varices, HCC, sclerotherapy and spleenectomy were significantly presented in patients with PVT. Also, elevated liver enzymes, bilirubin and alpha fetoprotein were significantly increased in them in comparison with those without PVT. Historically, patients with PVT were considered to be at increased risk of mortality related to bleeding complications, but improvements in the prophylactic management of esophageal varices have significantly reduced these risks. Conversely, patients with occlusive PVT can be difficult to manage with respect to ascites and hepatohydrothorax. (2)

The present study showed that 62.9% from cirrhotic patients with portal vein thrombosis were Child class C and 33.70 were Child class B. [29] reported that portal vein thrombosis usually occurs in Child B or C patients with cirrhosis and it is not always easy to attribute specific symptoms or deteriorating clinical condition to either worsening of the cirrhosis or to the de novo occurrence of portal vein thrombosis. Our study has relation with [30] who found 52 % of cirrhotic patients with portal vein thrombosis were child C. [21] reported that advanced liver failure has shown

to associated with an increased risk for developing non tumoral portal vein thrombosis.

Portal vein and spleenic diameter,were significantly increased in patients with PVT in comparison with those without PVT. [30]. found that oesophageal varices was present in 94% of cirrhotic patients with portal vein thrombosis. splenomegaly and portal hypertention in our patients may be due to other associated factors rather than cirrhosis and portal vein thrombosis such as bilhaziases which have wide spread in Egypt .

Retrograde flow, distention and increased echogenicity at the site of the thrombus in addition to cavernous transformation were significantly observed on Doppler examination of patients with PVT. On PVT, 2 compensatory mechanisms occur first mechanism is "arterial vasodilation" of the hepatic artery, "arterial rescue" The second compensatory mechanism is "venous rescue", consisting of the rapid development of collaterals to bypass the obstru-zcttion. called "cavernoma", connecting the two patent portions proximally and distally to the thrombus. Usually, the original portal vein becomes a thin, fibrotic cord, which is dificult to visualize . At this stage, the development of a hyperkinetic circulation, characterized by low systemic vascular resistance and a high cardiac output. Impairment of portal flow has important consequences on liver tissue. It has been demonstrated that the progressive obliteration of the portal vein stimulates apoptosis of hepatocytes in the hypoperfused lobe (3).

Finally, we concluded that PVT is frequently reported in patients with liver cirrhosis especially those with advanced stages as a part from a complex scenario , as PVT may a result of several risk factors but definitely, it is associated with poor outcome.

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