FIBRINOLYTIC ACTIVITY IN HEPATOCELLULAR CARCINOMA

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Received for Puplication : 10/1/1992

ABSTRACT

The observed effect of hepatocellualr carcinoma on the fibrinolytic system is contradictory. This lead us to study the changes in fibrinolytic activity in 13 patients of hepatoma compared to 10 controls.

Our patients especially the yroup with evidence of liver cirrhosis showed significant; hypofibrinogenaemia, increase in fibrinogen degradation products (FDPs), prolongation of prothrombin & thromhin time. and over-all reduction in prothrombin concentration. In addition there was also significant thrombocytopaenia.

Such alterations favor the assumption of increased fibrinolysis and/or dissiminated intravascualr coagulation which are important factors in the pathophysiological mechanisms underlying the haemorrhagic diasthesis in patients with hepatocellular carcinoma.

INTRODUCTION

Substantial evidences have been accumulated indicating that cancer patients are at high risk for bleeding and thrombosis. virtually every haem-

ostatic function may be disturbed by severe liver dysfunction (Ratnoff, 1963). However, the effect of hepatocellualr carcinoma on the fibrinolytic system is contradictory. Owen & Bowie (1977) found elevated FDPs in a substantial percentage of patients and assumed subclinical consumptive coagulopathy or chronic dissiminated coagulopathy (DIC), on the contrary, Van der Walt et al. (1977) could not found a definite diagnosis or DIC in hepatoma patients.

The precise effects of hepatocellualr carcinoma on the clotting system are uncertain (Imaoka et al., 1986).

The present study aimed to clarify the effect of hepatocellualr carcinoma on the fibrinolytic system and its relation to the bleeding tendency in such patients.

MATERIAL AND METHODS

The present study comprised 13 patients: 8 male and 5 females with age ranging from 45-70 years. The diagnosis of hepatoma is based on clinical palpation of hard mass or masses. sonography by hypodense areas and pathologically by biopsy from the hepatic mass.

The total group was subdivided by liver biopsy into two subgroups:

I) Hepatoma without evidence of liver cirrhosis.
2) Hepatoma with evidence of liver cirrhosis.

Ten healthy subjects (6 males and 4 females with age ranging from 20 to 60 years) were taken as a control group.

For the patients and the controls, the following were performed: through clinical examination, routine urine and stool analysis, full blood picture including platelet count according to Brecher et al. (1950). liver function tests including total protein (Gornall, 1968), serum albumin (Drupt, 1974), serum bilirubin (Jendrassik, 1938), SCOT & SGOT (Reitman & Frankel, 1957), S. Alkaline phosphatase (Belfield & Goldberg, 1971), determination of prothrombin time & pro-

thrombirl concentration (Quick, 1938), determination of thrombin time (Robertson et al., 1975), determination of fibrinogen (modified Claus, 1957), determination of fibringen degradation products using staphylococcus clumping test (Hawiger et al., 1970), Ultrasonography and Liver biopsy.

RESULTS

Clinical data are tabulated in table (1), some liver function tests In table (2). fibrinolytic activity in tables (3-5), and correlation between fibrinogen and FDPs table (6).

DISCUSSION

Bleeding is a serious complication endangering life in patients with liver disease, since both cloting factors and platelets may be quantitatively or qualitatively defective.

Endogenous anticoagulant substances, activation of fibrinolytic system and consumption coagulopathy have been accused (Omran & El-AShmawy, 1979; Abdel Wahab, 1982, biema et al., l985 and Madkour et al., 1985b).

The present work showed decrease of the level of fibrinogen in the total group of patients with hepatoma when compared to the controls, and this reduction was more In the subgroup of hepatoma with evidence of liver- cirrhosis than those without evidence of liver cirrhosis (tables 3-5). Our results are in agreement with Owen and Bowie (1977), and Imaoka et al. (1986), who reported hypofibrinogenaemia in solid hepatic tumor with wide spread metastases and attributed it to consumptive coagulopathy. and the more decrease in fibrinogen in the subyroup of hepatoma patients with liver cirrhosis is a logic result secodnary to liver cirrhosis.

On the contrary, Kwan et al. (1959), Miller et al., (1967), and Van Der Walt et al., 1977) reported an increased levels of fibrinogen in patients with hepatic cancer and they attributed it to a non specific response to tumour tissue, with extrahepatic reticuloendothelial fibrinogen production.

Kies et al. (1980) reported that most of cancer patients with or without hepatic involvement are able to maintain normal or near normal hemostatic function in vitro, untill advanced stage of the disease, they reported that deviation from normal for prothrombin time, partial thromboplastin time or thrombin time, decreased antithrombin III activity or increased FDPs signals the presence of complicating pathophysiologic event such as dissiminated intravascular coagulation or cirrhosis. Decreased fibrinogen level or antithromnin III and elevation or FDFs are more sensitive indicator of dissiminated intravascualr coagulation than prolongation of prothrombin time, partial thromboplastin time or thrombin time.

The present work showed a highly significant increase in FDPs in the total group of patients with hepatoma, and the increase was more manifest in patients with evidence or liver cirrhosis than those without evidence of cirrhosis (tables 3-5).

In hepatic disorders, vitamin K dependent factors II. VII, IX, X cause abnormalities in both extrinsic and intrinsic pathways resultiny in prolongation of prothrombin time and partial thromboplastine time. Vitamin K dependent fatcros were reduced due to either failed synthesis or impaired absorption of vitamin K.

Ratnoff, (I963) and Spector et al. (1966) reported that the thrombin time is often prolonged in hepatic disease. Van Der Walt et al., (I977) in their study for assesment of haemostasis in patients with liver cancer, found that the patients as a whole showed prolonged prothrombin time and increased level of fibrinogen. However thrombin time and platelets count were not significantly altered.

This work showed prolongation of prothrombin time & thrombin time, and overall reduction in prothrombin concentration in hepatoma patients and its subgroups (tables 3-5).

Also there is significant thrombocytopenia in the group of hepatoma patients and its subgroups when com-

pared to normai controls (Tabies 3-5), and this is in agreement with the findings of Penny et al., (1966). This could be attributed to decreased production. increased destruction by non endothelialized endovascualr surface, increased splenic sequestration or combination of these factors.

Correlative study showed an inverse correlation between fibrinogen and FDPs in hepatoma patients and its subgroups (hepatoma without liver cirrhosis and hepatoma with liver cirrhosis), table (6). This can be explained by enhanced fibrinolysis and/or dissiminated intravascualr coagulopathy.

These data together favour the assumption of increased fibrinolysis. and/or dissiminated intravascular coagulation which is more obvious in the subgroup of hepatoma with evidence of liver cirrhosis indicating that liver cell dysfunction is a major aetiological factor in the pathophysiological mechanisms underlying the disturbed fibrinolytic activity.

From these results, it could be concluded that the enhancement of fibrinolytic activity and/or dissiminated intravascular coagulation are important factros in the pathophysiological changes underlying the haemorrhagic diasthesis in patients with hepatocellular carcinoma.

Table (1) : Clinical data in patients with hepatoma.

Age	Sex	Jaundice	Bleeding disorder	Clinical and ultra sonography			Liver biopsy
				Liver (Site of mass)	Spleen	Ascites	
60 Y		+	-	Englarged 2 masses in left lobe. not tender	Enlarged	+	Hepatoma grade I
56 Y		+	-	One mass in the right lobe, liver enlarged firm. not tender	Enlarged	-	Hepatoma grade I
55 Y		-	-	Enlarged, firm not tender right lobe	Normal size	-	Hepatoma grade I
70 Y		+	Purpuric eruption over the abdomen and lower limb bilaterally	One mass in the left lobe	Enlarged	+	Hepatoma grade II
45 Y		+	-	Multiple masses in the right lobe, firm enlarged liver	Hugely enlarged	+	Hepatoma grade I
48 Y		+	-	One mass in the left lobe	Normal size	-	Hepatoma grade I
50 Y		+	-	One mass in th right lobe	Normal size	+	Hepatoma grade II
50 Y		+	-	Multiple masses in both, not tender, enlarged liver	Enlarged	-	Hepatoma grade II
57 Y		-	-	Enlarged, firm liver with one mass in the left lobe	Normal size	-	Hepatoma grade I

Cont.

Age	Sex	Jaundice	Bleeding disorder	Clinical and ultra sonography			Liver biopsy
				Liver (Site of mass)	Spleen	Ascites	
65 Y		+	Purpuric eruption over abdomen and lower limb bilaterally	Enlarged not tender with one mass in the left lobe	Normal	-	Hepatoma grade I
63 Y		+	-	Multiple masses enlarged in both lobes, enlarged liver	Enlarged	+	Hepatoma grade II
60 Y		-					
70 Y		+	-	Enlarged, multiple masses in the both lobes	Splenectomy	++	Hepatoma grade II
			Attack of haematemesis	Enlarged, multiple masses in the both lobes	Splenectomy	+	Hepatoma grade III

Table (2) : Some liver function tests in hepatoma patients versus controls.

		Total protein (gm/100ml)	Serum albumin (gm/100ml)	Serum albumin (mg/l)	SGOT (unit/ml)	SGOT (unit/ml)	Alkaline phosphatase (king armstrong u/100ml)
Control	M	7	4.43	0.63	26.3	22.3	7.22
n = 10	SD±	0.55	0.32	0.15	2.16	2.45	1.86
Hepatoma	M	7.21	3.53	2.25	69	38.92	24.95
n = 13	SD±	0.94	0.79	1.21	23.27	58.70	5.98

Table (3) : Comparative evaluation of some of the fibrinolytic activities between total group of hepatocelluair carcinoma and its subgroups versus controls.

	Fibrinogen		P. D. Ps.		protrombin tim		Prothrombin concetration		Thrombin time		Platelet count	
	M	±SD	M	±SD	M	±SD	M	±SD	M	±SD	M	±SD
Control group n = 10	292.4	39.75	4.2	1.55	12.65	0.70	92.3	5.31	10.8	1.16	211	15.24
Total hepatoma n = 13	145.615	27.17	42	7.32	14.31	1.11	75.69	11.24	16.54	4.16	124.231	49.99
P_1	H. S.		H. S.		H. S.		H. S.		M. S.		M. S.	
Hepatoma without liver cirrhosis n = 6	155.17	23.56	28.8	10.33	14.33	1.51	76.17	14.13	15.17	2.56	150	41.71
P_2	H. S.		H. S.		H. S.		H. S.		H. S.		H. S.	
Hepatoma with evidence of liver cirrhosis n = 7	137.43	29.06	51.43	32.28	14.29	0.76	75.29	9.25	17.71	5.057	102.14	48.12
P_3	H. S.		H. S.		H. S.		H. S.		H. S.			

n = Number of the cases
H. S. = Highly significant < 0.001
M. S. = Moderate significant < 0.01
Mild. Sig. = Mild significant <0.05.

P_1 = P-value between total group versus controls.
P_2 = P-value between subgroup without liver cirrhosis versus controls.
P_3 = P-value between subgroup with liver cirrhosis versus controls.

Table (4) : Comparative evaluation of some of the fibrinolytic activities between subgroups of total hepatoma versus total hepatoma.

	Fibrinogen		P. D. Ps.		protrombin tim		Prothrombin concetration		Thrombin time		Platelet count	
	M	±SD	M	±SD	M	±SD	M	±SD	M	±SD	M	±SD
Total hepatoma n = 13	145.615	27.17	42	7.32	14.31	1.11	75.69	11.24	16.54	4.16	124.231	49.99
Hepatoma without liver cirrhosis n = 6	155.17	23.56	28.8	10.33	14.33	1.51	76.17	14.13	15.17	2.56	150	41.71
P_1	N. S.		N. S.		N. S.		N. S.		N. S.		N. S.	
Hepatoma with evidence of liver cirrhosis n = 7	137.43	29.06	51.43	32.28	14.29	0.76	75.29	9.25	17.71	5.057	102.14	48.12
P_2	N. S.		N. S.		N. S.		N. S.		N. S.		N. S.	

n = Number of cases
N. S. = Non Significant > 0.05.

P_1 = P-value between total group versus the subgroup without liver cirrhosis.
P_2 = P-value between total group versus the subgroup with liver cirrhosis.

Table (5) : Comparative evaluation of some of the fibrinolytic activities between subgroups of hepatoma without liver cirrhosis versus hepatoma with liver cirrhosis.

	Fibrinogen		P. D. Ps.		protrombin tim		Prothrombin concetration		Thrombin time		Platelet count	
	M	±SD	M	±SD	M	±SD	M	±SD	M	±SD	M	±SD
Hepatoma without liver cirrhosis n = 6	155.17	23.56	28.8	10.33	14.33	1.51	76.17	14.13	15.17	2.56	150	41.71
Hepatoma with evidence of liver cirrhosis n = 7	137.43	29.06	51.43	32.28	14.29	0.76	75.29	9.25	17.71	5.057	102.14	48.12
P-value	N. S.		N. S.		N. S.		N. S.		N. S.		N. S.	

n = Number of cases
N. S. = Non Significant > 0.05.

Table (6) : Correlation between fibrinogen degradation products and fibrinogen in total group and its subgroups.

Total hepatoma		
r. value		- 0.6
Subgroups of total hepatoma :		
1st subgroup :	Hepatoma without	liver cirrhosis
	r. value	- 0.26
2nd subgroup :	Hepatoma with	liver cirrhosis
	r. value	- 0.8

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