Hemostatic Derangements in Patients with Solid Malignant Tumors

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ABSTRACT

BACKGROUND: Cancer patients show an increased susceptibility to thromboembolic diseases. Although clinical symptoms occur less frequently, disorders of coagulation are very common in cancer patients. The aim of the study was to determine the presence of hemostatic derangements in patients suffering from solid malignant tumors.

METHODS: This case-controlled study was conducted on patients with solid malignant tumors who presented to Al-Yermok Teaching Hospital and Hospital of Radiation and Nuclear Medicine in Iraq, from January 2004 to July 2004. Forty cases were included in the study and the control group included fifteen age and gender matched healthy volunteers. Platelet count was determined from blood sample, while tests for prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen and D-dimer were conducted on plasma.

RESULTS: Fourteen patients had slight concurrent bleeding; only one patient gave history of recurrent attacks of deep venous thrombosis. The most common hemostatic abnormalities were elevated D-dimer (45%, n=18), thrombocytosis (27.5%, n=11), prolonged TT (25%, n=10) and hyperfibrinogenemia (25%, n=10).

The mean PT, aPTT and TT were higher in subjects with malignancies as compared to the healthy controls; and these variables were also higher in those with evidence of intravascular coagulation and fibrinolysis (ICF) as compared to those without ICF syndrome. The mean fibrinogen level and platelet count were higher in patients with malignancy (mean=3.1 g/L) and (mean=317.8 x 109/L) as compared to healthy controls (mean=3 g/L and mean=260.7 x 109/L) respectively where the (p=0.02 and p=0.08) respectively; moreover, the mean of platelets tended to be lower when there was evidence of decompensated type ICF (mean=125 x 109/L), rather than compensated type (mean=171.4 x 109/L) or over compensated type (mean=491.4 x 109/L). The rate of occurrence of ICF syndrome was not significantly higher with adenocarcinoma than that with other histologic types (p=0.18). On the other hand, this rate was significantly higher with high grade tumor than with low grade tumor and in patients with distant metastasis (p=0.001).

CONCLUSION: Hemostatic derangement is common in patients with a wide variety of malignancies. The plasma D-dimer test with other indices of DIC syndrome forms a good and simple applicable panel of tests for assessment of ICF syndrome.

Keywords: Hemostatic derangement; Solid malignant tumor; D-dimer

INTRODUCTION

Patients with solid malignant tumor show an increased susceptibility to thromboembolic events as compared to the general population. Although clinical symptoms occur less frequently, disorders of coagulation are very common in such patients [1]. Thromboembolism is one of the most common causes of death in cancer patients [1]. Ovarian, pancreatic, prostatic and lung cancer, and mucin-producing carcinomas of gastrointestinal tract are among the malignancies most frequently associated with thromboembolic episodes [1].

The overall incidence of clinical thromboembolic disease (TED) in patients with cancer has been reported to vary between 1% and 11% [2]. The incidence of TED in postmortem studies of cancer patients is considerably higher. In one prospective study, Ambrus and associates

reported that thrombosis and/or bleeding were the second most common cause of death in hospitalized cancer patients [3]. An abnormal result on routine tests of blood coagulation in cancer patients has been reported to occur in as many as 92% of the patients [4, 5]. A wide range of coagulation disturbances can occur in patients with malignancies, which can predispose patients to hemorrhage or thrombosis [6].

In 1974, the concept of "intravascular coagulation and fibrinolysis syndrome (ICF)" was introduced by Owen and Bowie and the purpose was to examine the incidence and type of hemostatic derangement in patients with cancer [7]. Cooper and associates classified this syndrome into three groups; decompensated which is defined by depressed platelets or fibrinogen levels along with other hemostatic abnormalities, compensated in which platelets or fibrinogen values are normal but other hemostatic tests are abnormally prolonged, and overcompensated whereas the platelets or fibrinogen are increased together with other hemostatic abnormalities. This has also been correlated with the conventional terms; acute, sub-acute and chronic DIC with decompensated, overcompensated and compensated DIC respectively [7, 8].

The aims of the study were to determine the presence of hemostatic derangements in patients suffering from solid malignant tumors. A secondary aim was to elucidate the association of intravascular coagulation and fibrinolysis (ICF) with grade of tumor, histologic type of tumor and presence of metastasis.

METHODS AND MATERIALS

This case-controlled study was conducted during a period of six months, from January to July 2004. A total of 40 patients with solid malignant tumors of various organs were included in this study; 13 of these patients were admitted to Al-Yermok Teaching Hospital in Baghdad and 27 patients were from the Hospital of Radiation and Nuclear Medicine in Baghdad. Fifteen age and sex matched healthy volunteers were included in this present study as control group, 9 males and 6 females, the age range was 40-70 years for males and 40-60 years for females.

After taking consent, data was collected on a questionnaire including the complete history of the disease, clinical findings on physical examination, with special attention to any evidence of increased bleeding or clotting tendency at enrollment or in the past since the diagnosis of malignancy; details regarding the tumour including grade, histologic type and distant metastasis; and laboratory data. All laboratory tests were performed in Al-Yermok Teaching Hospital Laboratory.

We excluded patients with co-morbid conditions that could affect coagulation profile, or patients using certain medication or those with history of coagulation disorders. The platelet count was conducted on blood whereas plasma was isolated for remaining laboratory tests including prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen and D-dimer. Patients were considered to have evidence of intravascular coagulation and fibrinolysis (ICF) syndrome if their plasma D-dimer level was more than 0.5µg/ml.

The concept of ICF of Owen and Bowie was adopted and their classification of overcompensated, compensated and decompensated ICF was tested [8, 9] and an attempt was made to identify those key tests that might enable us to discover patients with coagulation problems. The D-dimer and platelets were used as indicators and separated the patients into four groups.

1. Patients with no ICF (normal D-dimer).
2. Those with overcompensated ICF (elevated D-dimer and elevated platelets count).
3. Those with compensated ICF (elevated D-dimer but normal platelets count).
4. Those with decompensated ICF (elevated D-dimer and decreased platelets count).

A battery of hemostatic tests were applied among these four groups, and several tests appeared to be helpful in differentiating those with no ICF, compensated ICF, overcompensated ICF and decompensated ICF. These were PT, APTT, fibrinogen level and TT.

In this study, the FDP test which was used by Owen and Bowie study [7] has been replaced by D-dimer test for the diagnosis of ICF syndrome because the D-dimer test is regarded now to be more specific for fibrin degradation products whereas the formation of fibrinolytic degradation products (FDP), X, Y, D and E fragments may be either fibrinogen or fibrin derived following the plasmin digestion [9, 23]. Moreover, the criteria of Owen and Bowie for the diagnosis of ICF was utilized, although in recent years many new criteria were added to diagnose ICF [11, 12, 13] but none of these were applicable in the present study because of the non-availability of some of relevant laboratory tests.

Pooled plasma from at least 4 healthy individuals, were prepared and divided into

aliquots each contains 1 ml, stored at – 20C° to be used simultaneously with patients plasma for a period not exceeding 10 days. Positive and negative control plasma (for D-dimer test) was supplied with plasma D-dimer kit.

The reference range of the hematological tests were platelet count 150000 – 400000, PT was 12 – 15 seconds, PTT was 32– 39 seconds, TT was 13 – 17 seconds, fibrinogen was 2.52-3.64 g/L, plasma D-dimer concentration < 0.5µg / ml.

Data were entered into a computerized database structure. Statistical analysis were done using SPSS version 10. The statistical significance of difference in rate of an outcome between 2 groups was assessed by Fisher´s exact significance test, while between more than 2 groups the likelihood test was used. The statistical significance of difference in mean of a continuous variable between 2 groups was assessed by t-test and between more than 2 groups by ANOVA test.

The difference in median of an ordered variable (like D-dimer) between 2 groups was assessed by Mann-Whitney test and between more than 2 groups by Kruskal-Wallis test.

Spearman´s rank was used to study the strength of association (linear correlation) between D-dimer as an ordered variable and other continuous variables. P value of less than 0.05 was considered statistically significant.

RESULTS

Forty patients were included in the malignancy group and 15 healthy controls were selected.

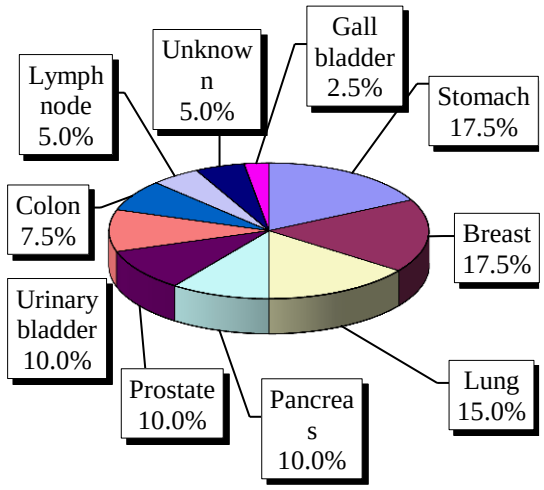
Table 1: Coagulation profile for malignancy cases and healthy control subjects

Coagulation profile*	Healthy controls (n=15)	Malignancy (n=40)	p-value
Platelets count (x 109/L)	260.7 ±7.96	317.8 ± 23.46	0.02
PT (sec.)	12.9 ±0.27	15 ±0.32	<0.001
PTT (sec.)	35.1 ±0.56	37.9±0.31	<0.001
TT (sec.)	14.4±0.39	16±0.56	0.02
Fibrinogen (g/L)	3±0.08	3.1±0.15	0.66
D-dimer conc. (µg/ml)1	<0.5 (<0.5 to <0.5)	2-4 (<0.5 to 4-8)	0.002

* The values are mean ± standard error (SE) except for D-Dimer concentration.

[1]Median (range) is provided for D-dimer. (PT=Prothrombin time, PTT= partial thromboplastin time, TT=thrombin time)

Figure 1: Pie chart showing the frequency distribution of cases by site of primary tumor



Thirteen of these patients were admitted to Al-Yermok Teaching Hospital in Baghdad, and the other 27 were recruited from the Hospital of Radiation and Nuclear Medicine in Baghdad. 26 were males (65%) in the malignancy group.

The frequency distribution of age and sex in healthy controls and malignant cases are shown in Table 3. There were 26 males (65%) and 14 females (35%), their age ranged from 36 to 73 years for males and from 38 to 70 years for females. The primary sites of malignant disease and their frequency distribution are shown in Figure 1. The most frequent histologic types were adenocarcinoma, 29 patients (72.5%), transitional cell carcinoma, 4 patients (10.0 %), undifferentiated small cell carcinoma, 2 patients (5.0%), non–Hodgkins lymphoma, 2 patients (5.0%) and large cell carcinoma, 1 patient (2.5%).

Among the forty cases, 6 (15%) had grade I, 17 (42.5%) had grade II, 12 (30%) had grade III, and 5 (12.5 %) had grade IV tumors, as determined by histology. In about half of the patients (55%, n=22), distant metastasis was present. Thirty-five percent (n=14) patients had slight concurrent bleeding; in 10 of them the bleeding was related to their malignant disease. These were gastrointestinal bleeding from carcinoma of the stomach and colon (n=2), hematuria from carcinoma of the prostate and urinary bladder (n=6) and hemoptysis from the carcinoma of the lung (n=2). While in the other 4 cases, the bleeding was not related to their malignant disease; these were epistaxis, bruising, ecchymosis and vaginal bleeding from the carcinoma of the breast, gall bladder and non –

Hodgkin lymphoma. The evidence of thrombosis was encountered in one patient only.

All patients were classified according to the results of D-dimer into 2 groups; those with negative D-dimer (considered having no evidence of ICF syndrome), this group consists of 22 patients (55% of cases) and those with positive D-dimer (considered having evidence of ICF syndrome), this group consists of 18 patients (45% of cases).

As compared to the healthy controls, PT ($p<0.001$), aPTT ($p<0.001$) and TT ($p=0.02$) were significantly higher in patients with malignancy (Table 1). These variables were also higher in those with evidence of ICF as compared to those without ICF syndrome (Table 2). Platelet count was significantly higher in patients with malignancy as compared to that in healthy controls ($p=0.02$) (Table 1). Although lower in ICF patients, the platelet count in patients without ICF was not significantly different from that in patients with ICF ($p=0.24$). Moreover, the platelet count tended to be lower when there was evidence of ICF of the decompensated type rather than compensated or overcompensated types as depicted in Table 2 ($p<0.001$). Fibrinogen level was lower in those with ICF ($p<0.001$) (Table 2). Although not statistically significant, fibrinogen level was slightly lower in decompensated state (2.3±0.3g/L) as compared to compensated (2.6±0.3g/L) and overcompensated ICF states (2.6±0.4g/L) ($p=0.62$) (Table 2). In this study, 10% (n=4) of cancer patients were diagnosed as decompensated ICF based on prolongation of PT, APTT, low platelet count and/or hyperfibrinogenemia and a positive D-dimer, but 5% (n=2) patients had normal fibrinogen level.

Except for D-dimer concentration, the absence, presence of either high-grade tumor or distant metastasis or else the presence of both of these were not associated with a deranged coagulation profile (Table 3). All patients with thrombocytopenia were those with high grade tumors and not low grade tumors ($p=0.009$). On the other hand, more subjects with thrombocytosis had evidence of distant metastasis as opposed to the absence of metastasis (n=9 vs. n=2, $p=0.04$) (Table 4). Thrombocytopenia was observed in five (12.5%) cancer patients; in four of them, the D-dimer was positive, and therefore, they fit the criteria of decompensated ICF, while only one patient had decreased platelet count (30×10^9 /L) with negative D-dimer (Table 4). A total of 16.6% of the patients with positive D-dimer had low fibrinogen level, and as expected, all the patients had prolonged TT, while others had either high fibrinogen level (5.5%) or normal fibrinogen level (77.7%). Thirty-three percent patients with normal fibrinogen level and positive D-dimer also had prolonged TT.

The most common coagulation abnormalities in patients with malignancy were elevated D-dimer

Table 2: Coagulation profile for: A) ICF positive and negative malignancy cases, and B) 3 sub-classes of cases with ICF syndrome. (ICF=intravascular fibrinolysis, PT=Prothrombin time, PTT= Partial thromboplastin time, TT=Thrombin time)

A) ICF syndrome				B) Classification of ICF syndrome			
	Negative (n=22) (Group-I)	Positive (n=18)	p	Overcompen-sated (n=7) (Group-II)	Compensated (n=7) (Group-III)	Decompenstat-ed (n=4) (Group-IV)	p
Platelets count (x 10^9/L)	344.1±26.5	285.6±40.4	0.24	491.4±9.1	171.4±10.6	125.0±6.5	<0.001
PT (sec.)	14.2±0.4	16.1±0.5	0.003	16.3±0.7	16.1±0.9	16.5±0.7	0.82
PTT (sec.)	37.1±0.3	38.8±0.5	0.007	38.3±0.7	38.7±1.2	40±0.4	0.5
TT (sec.)	13.3±0.2	19.3±0.6	<0.001	19.3±0.4	19.9±1.5	20.0±1.0	0.65
Fibrinogen (g/L)	3.6±0.2	2.5±0.2	<0.001	2.6±0.4	2.6±0.3	2.3±0.3	0.62
D-dimer conc. (µg/ml)*	<0.5 (<0.5 to <0.5)	1-2 (0.5-1 to 4-8)	<0.001	1-2 (0.5-1 to 2-4)	1-2 (0.5-1 to 4-8)	2-4 (0.5-1 to 4-8)	0.62
Total (%)	22 (55)	18 (45)		7 (17.5)	7 (17.5)	4 (10)	

Table 3: Coagulation profile for: A) Presence of none, at least one, or both risk factors, high grade tumor and/or metastasis, in patients with malignancy (n=40)*; and B) D-dimer concentra -tion for healthy controls and malignant cases (n=55). (PT=Prothrombin time, PTT= Partial thromboplastin time, TT=Thrombin time)

	A) Risk factors (High grade and metastasis)*				B) D-dimer concentration ($\mu g/ml)^{-3}$ groups			
	Negative	At least one positive	Both high grade and metastasis	p*	Negative (<0.5)	Low conc. (0.5-2)	High conc. (>2-8)	p
Total No (%)	15 (37.5)	11 (27.5)	14 (35)	-	37 (67.2)	11 (20)	7 (12.8)	-
Platelets count (x 10^9/L)	350.7±22.1	325.5±53.2	276.4±47.2	0.5*	310.3±17.3	312.7±53.9	242.9±61.6	0.29
PT (sec.)	14.4±0.5	14.9±0.6	15.8±0.6	0.31*	13.7±0.3	15.3±0.5	17.3±0.7	0.001
PTT (sec.)	37.1±0.3	37.5±0.8	39.0±0.4	0.11*	36.3±0.3	37.6±0.6	40.7±0.4	<0.001
TT (sec.)	13.3±0.25	16.5±1.0	18.4±1.0	0.19*	13.7±0.2	18.0±0.5	21.3±1.0	<0.001
Fibrinogen (g/L)	3.5±0.2	3.0±0.3	2.7±0.3	0.42*	3.3±0.1	2.8±0.3	2.2±0.2	<0.001
D-dimer conc. (µg/ml)	<0.5 (<0.5 to <0.5)	0.5-1 (<0.5 to 2-4)	1-2 (<0.5 to 4-8)	0.04*	-	-	-	-

* P-value for section (A) of the table is for the difference between "at least one positive" category and "both, high grade tumor and distant metastasis present" category.

(45%, n=18), thrombocytosis (27.5%, n=11), prolonged TT (25%, n=10) and hyperfibrinogemia (25%, n=10). Thirty-two patients (80%) had two or more abnormal hemostatic tests (Table 4).

More subjects with adenocarcinoma had evidence of ICF as compared to those with other histologic types but this was not statistically significant (51.9%% vs. 30.8%, p=0.18) (Table 5). On the other hand, ICF was significantly more common in those with high grade tumor than those with low grade tumor (76.5% vs. 21.7%, p=0.001), and in patients showing distant metastasis as compared to those without distant metastasis (72.7% vs. 11.1%, p <0.001) (Table 5).

There was a moderately positive linear correlation (r=0.552) between D-dimer concentration and PT, and also a moderately positive linear correlation (r =0.578) between D-dimer and PTT and a strong positive linear correlation (r =0.875) between D-dimer and TT as shown in Table 6. There was a weak negative linear correlation (r= -0.259) between the platelet count and D-dimer concentration (Table 6). There was also a moderately negative linear correlation between D-dimer concentration and fibrinogen level (r= -0.614).

DISCUSSION

In this study, 32 patients with malignancy (80%) had two or more abnormal hemostatic tests. The most common abnormalities in patients with malignancy were elevated D-dimer (45%), thrombocytosis (27.5%), prolonged TT (25%) and hyperfibrinogenemia (25%). As compared to the healthy controls, platelet count, PT, aPTT and TT were significantly higher in patients with malignancy. Also, ICF was significantly more common in patients with high grade tumor than those with low grade tumor and in patients with evidence of distant metastasis as compared to those without distant metastasis.

Alterations of hemostasis commonly accompany the progression of malignant diseases and every known component of the hemostatic mechanism may be affected by these disease processes. Nearly all patients with an active neoplasm will exhibit at least subtle biochemical changes in hemostasis, and a few of them develop clinically evident thrombosis or hemorrhage [14].

The most common abnormalities in patients with malignancy were elevated D-dimer, thrombocytosis, prolonged TT and hyperfibrinogenemia. These results are comparable with results of a previous study [5]. These abnormalities are consistent with the presence, in cancer patients, of an "overcompensated intravascular coagulation with fibrinolysis (ICF)". It is hypothesized that low-grade intravascular coagulation with accelerated clotting factor utilization is accompanied by increased synthetic rate for fibrinogen, clotting factors and platelets, resulting in actual increase in their levels in the circulation [15].

In the present study, 80% of the patients had two or more abnormal test results, which is lower

Table 4: Association between the rates of abnormal coagulation parameters and characteristics of tumor

Patient Statistics n (%)	Thrombocytosis	Hyperfibrinogenemia	Thrombocytopenia	Hypofibrinogenemia	Prolonged PT	Prolonged PTT	Prolonged TT	Positive D-dimer	Total cases with malignancy
Total	11 (27.5)	10 (25)	5 (12.5)	3 (7.5)	7 (17.5)	9 (22.5)	10 (25)	18 (45)	40 (100)
Grading of tumour									
Low grade (I-II)	6 (26.1)	8 (34.8)	0 (0)	1 (4.3)	3 (13)	1 (4.3)	2 (8.7)	5 (21.7)	23 (57.5)
High grade (III-IV)	5 (29.4)	2 (11.8)	5 (29.4)	2 (11.8)	4 (23.5)	8 (47.1)	8 (47.1)	13 (76.5)	17 (42.5)
P (Fisher's)	0.55	0.1	0.009	0.38	0.33	0.002	0.008	0.001	
Distant metastasis									
Negative	2 (11.1)	6 (33.3)	1 (5.6)	0 (0)	3 (16.7)	2 (11.1)	1 (5.6)	2 (11.1)	18 (45)
Positive	9 (40.9)	4 (18.2)	4 (18.2)	3 (13.6)	4 (18.2)	7 (31.8)	9 (40.9)	16(72.7)	22 (55)
P (Fisher's)	0.04	0.23	0.24	0.16	0.62	0.12	0.01	<0.001	
Risk factors (Metastasis and high grade tumour)*									
Negative	2 (13.3)	6 (40)	0 (0)	0 (0)	2 (13.3)	0 (0)	0 (0)	0 (0)	15 (37.5)
At least one +ve	4 (36.4)	2 (18.2)	1 (9.1)	1 (9.1)	2 (18.2)	3 (27.3)	3 (27.3)	7 (63.6)	11 (27.5)
Both high grade and metastasis	5 (35.7)	2 (14.3)	4 (28.6)	2 (14.3)	3 (21.4)	6 (42.9)	7 (50)	11 (78.6)	14 (35)
P (Fisher's)*	0.65*	0.6*	0.24*	0.59*	0.62*	0.35*	0.23*	0.35*	
D- Dimer concentrations									
Negative (<0.5)	4 (18.2)	9 (40.9)	1 (4.5)	0 (0)	2 (9.1)	0 (0)	0 (0)	-	22 (55)
Low conc. (0.5-2)	5 (45.5)	1 (9.1)	2 (18.2)	1 (9.1)	1 (9.1)	2 (18.2)	4 (36.4)	-	11 (27.5)
High conc. (>2-8)	2 (28.6)	0 (0)	2 (28.6)	2 (28.6)	4 (57.1)	7 (100)	6 (85.7)	-	7 (17.5)
P (Likelihood)	0.26	0.01	0.2	0.04	0.02	<0.001	<0.001	-	

Note: All of the values are expressed as n (%), except p-values
* p-value for "risk factors" is for the difference between "at least one positive" category and "both, high grade tumor and distant metastasis present" category
(PT=Prothrombin time, PTT= partial thromboplastin time, TT=thrombin time)

than that in a previous study [5] which showed a frequency of 92%. This variation probably can be explained by the differences in type of patients studied because all of the patients in the previous studies were referred to the oncology service as inoperable patients. These studies had a higher percentage (81%) of metastatic disease as compared to our patient sample (55%). Nevertheless, both studies indicated that hemostatic derangement was quite common in cancer patients. The frequency of positive D-dimer test in patients with solid malignant tumors was 45%, which is lower than that in the study conducted by Wilde JT, et al [16], that showed a frequency of 71%. This variation may be explained by the differences in type of patients studied, duration of illnesses and extent of the disease.

There was a statistically significant difference in the mean platelet count (p=0.02) between patients with malignancy and the healthy controls. Moreover, in the decompensated state, the mean platelet count was lower as compared to the platelet count in compensated and overcompensated states (p<0.001), and this finding validates a similar finding in a previous

Table 5: ICF syndrome and characteristics of tumor

	Positive ICF syndrome n=18 (45%)	Total malignancy cases n=40
Histologic type of tumour		
Adenocarcinoma	14 (51.9)	27
Others	4 (30.8)	13
P (Fisher's)	0.18	
Grading of tumour		
Low grade (I-II)	5 (21.7)	23
High grade (III-IV)	13 (76.5)	17
P (Fisher's)	0.001	
Distant		
Negative*	2 (11.1)	18
Positive*	16 (72.7)	22

*Negative=without distant metastasis, Positive= with distant metastasis. (ICF=intravascular fibrinolysis)

Table 6: Correlation between D-dimer, hist-ologic grading of tumor and coagulation parameters

Spearman's rank	D-dimer concentration	Histologic grading of tumor
Platelets count	-0.259	-0.235
PT (sec.)	.552(**)	0.065
PTT (sec.)	.578(**)	.504(**)
TT (sec.)	.875(**)	.426(**)
Fibrinogen (g/L)	-.614(**)	-.329(*)
D-dimer concentration (µg/ml)	1	.532(**)
Histologic grading of tumour	.532(**)	1

Note:- **: p <0.01
*: p<0.05
(PT=Prothrombin time, PTT=Partial thromboplastin time, TT=Thrombin time)

study [5].

Thrombocytopenia was observed in five (12.5%) cancer patients. In four of them, the D-dimer was positive, and therefore, they fit the criteria of decompensated ICF, while only one patient had decreased platelet count (30 X 10^9 /L) with negative D-dimer. This later patient was a case of non-Hodgkin's lymphoma and had presented with massively enlarged spleen. Splenic pooling and marrow involvement by the disease process are the possible causes for decreased platelet count in this patient.

Thrombocytosis was observed in 27.5% (n=11) of the cancer patients, a finding which is consistent with previous studies [4, 5, 17, 18]. In all of these studies, the frequency of thrombocytosis ranged between 25% and 60% [4, 5, 17, 18]. This thrombocytosis, which occurs much more frequently in untreated cancer patients than that in those undergoing treatment for cancer, may be explained by the existence of low-grade DIC, thrombocytolysis and overcompensation. Indeed, thrombopoietic activity has been recovered from the serum of patients with cancer having thrombocytosis [19], suggesting the existence of aberrancy in the usual relationship between platelet count and the production of thrombopoietin in some individuals with cancer.

The mean PT and mean aPTT were significantly higher in malignancy cases as compared to healthy controls (p <0.001 and <0.001, respectively), and was also significantly higher in cases with positive D-dimer as compared to those with negative D-dimer (p= 0.003 and 0.007, respectively). Although mean PT and aPTT were higher in decompensated ICF as compared to the compensated and the overcompensated ICF states, the difference were not statistically significant (p=0.82 and 0.5, respectively). These results are in agreement with the result of another study [9]. The mean TT was significantly higher in malignancy cases compared with healthy control (p=0.02), and it was also significantly higher in cases with positive D-dimer compared to those with negative D-dimer (p<0.001), which is consistent with the results of a previous study [5].

The products of fibrin breakdown interfere with fibrin monomers polymerization leading to the prolongation of TT [20]. Mean fibrinogen level was significantly lower in D-dimer positive cases than that in the D-dimer negative malignancy cases (p <0.001). Negative D-dimer in healthy controls in this study and a previous study [16] indicate that plasma D-dimer may be specific for fibrinolysis [10, 21-23].

In this study, 10% (n=4) of cancer patients were diagnosed as decompensated ICF based on prolongation of PT, APTT, low platelet count and/or, hyperfibrinogenemia and positive D-dimer, but half (n=2) of these patients had normal fibrinogen level. This can be explained by an increased fibrinogen production as a result of the underlying disorder and therefore, the increased fibrinogen consumption may not be sufficient to decrease fibrinogen below normal levels early in the decompensated ICF state. As the normal half-life of fibrinogen is approximately 4 days, a 50%

or greater decrease in fibrinogen level over one-day is compelling evidence supporting DIC or fibrinolysis, regardless of the final value being normal range [24].

In this study, there was not a significant association between the histological type of tumors and positivity of D-dimer (p=0.18), which is also consistent with a previous study [5], in which there was no relationship between the histological type and the elevation of FDP. However, there was an association between grade of tumors and the positivity of D-dimer. As compared to low grade tumors, more patients with high grade tumors had positive D-dimer (p=0.001). An explanation for this association can be that the tumor cells can directly and/or indirectly activate the coagulation and fibrinolysis systems. It is well-known that most tumor cells can express, on their surface, all proteins necessary for regulating the fibrinolytic pathways. Both, tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), as well as their inhibitors, are expressed in various kinds of tumor cells lines. The expression of uPA seems to be correlated with aggressiveness and histologic grade of tumors as well as clinical progression of different carcinomas [25].

More cases with distant metastasis had positive D-dimer (n=16/22, 72.2%) as compared to those without distant metastasis (n=2/18, 11.1%), (p<0.001). These are consistent with the result of a previous study [26], which showed that the D-dimer level was higher in patients with metastasis than those without metastasis, and that the high plasma D-dimer level is indicative of ongoing fibrinolysis within cancer tissues that occurs during tumor progression.

It should be noted that in spite of this evidence for the common occurrence of low-grade ICF in cancer patients, the occurrence of overt DIC, characterized by consumption of platelets and clotting factors with resultant bleeding complication, is uncommon, and DIC of clinical significant occurs in only 9%-15% of patients with cancer [27], which is comparable with findings obtained in the present study in which the percentage of clinical significant DIC was 10%.

Limitations of the study include small number of patients and non-application of more specialized tests and recent scoring system that are useful in the diagnosis of this syndrome such as measurement of soluble fibrin monomers and the sensitive assays that can measure the generation of thrombin fragment F1+2 or thrombin-antithrombin complex.

CONCLUSION

Disorders of hemostasis are present in a majority of patients with solid tumor malignancy. In a proper clinical setting, supported by abnormal hemostatic test results, the ICF syndrome should be suspected. Furthermore, precautionary measures can be taken to avoid its complication. Local or systemic activation of blood coagulation can be produced by tumor products and favors tumor spread, while interruption of blood coagulation reactions, in general, favors the host and impairs metastasis [27].

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