

Plasma D-dimer in Patients with Solid Malignant Tumors

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Abstract

Background: Cancer patients show increased susceptibility to thromboembolic disease, as compared with the general population, suggesting that disorders of coagulation are very common in this disease, although clinical symptoms occur less frequently. D-dimer test is simple and sensitive test to detect intravascular coagulation and fibrinolysis in patients with solid malignant tumors.

Objective: To identify those patients suffering from solid malignant tumors complicated with intravascular coagulation and fibrinolysis (ICF) by use of D-dimer, and the interrelation of plasma D-dimer level with histologic type of the tumor and metastasis.

Patients and methods: From January to July 2004, a total of 40 patients with solid malignant tumors of various tissues and of miscellaneous histopathologic type and grades. were included in this study, there were 26 males and 14 females, their age ranged from 36 to 73 years for males and from 38 to 70 years for females.

Thirteen of all patients were admitted to Al-Yarmouk Teaching Hospital and the other 27 patients were seen in the Hospital of Radiation and Nuclear Medicine clinics.

All patients were to have malignancy, and clinical information including full medical and surgical history as well as laboratory data were included from patients' files and formed the basis of this study. All patients were investigated for an "intravascular coagulation and fibrinolysis syndrome" (ICF) using D-dimer test on blood samples.

Results: The results presented in this study were based on analysis of 40 patients with solid malignant tumors, 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 .

D-dimer concentration in all healthy controls included in this study was negative (i.e. $<0.5 \mu\text{g/ml}$), and there was a statistically significant difference in the plasma D-dimer concentration between healthy control group and patients with solid malignant tumors (P value =0.002).

All patients were screened for ICF by the use of plasma D-dimer. Twenty two patients (55%) were found to have D-dimer $< 0.5 \mu\text{g/ml}$ (i.e no evidence of ICF syndrome) while 18 patients (45%) were found to have D-dimer $\geq 0.5 \mu\text{g/ml}$ (evidence of ICF syndrome).

Regarding the rate of positivity of D-dimer, it was more with adenocarcinoma than other types of solid malignant tumors but the differences failed to reach the level of significance (P value 0.18). On the other hand, this rate was more in patients showing distant metastasis and this difference was statistically significant (P value ≤ 0.001).

Conclusion: Plasma D-dimer test forms a good simple applicable test for assessment of ICF syndrome. Positive D-dimer test is higher in patients with solid malignant tumors compared to normal healthy controls and it is higher in patients with metastatic tumors compared to those with localized tumors and in adenocarcinoma in comparison with other histologic types.

Keywords: solid malignant tumors, intravascular coagulation and fibrinolysis (ICF), D-dimer

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Introduction

Activation of coagulation and fibrinolysis is known to be frequently associated with malignancy, although

the mechanism involved has not been fully clarified.

The extent of such activation has been reported to correlate with tumor stage and prognosis in some malignancies⁽¹⁾.

Cancer cells can activate the clotting system directly, thereby generating thrombin, or indirectly, by stimulating mononuclear cells to

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synthesize and express a variety of procoagulants⁽²⁾. In fact, tissue factors and cancer procoagulants are expressed in tumor cells, resulting in the activation of clotting factors VII and X⁽³⁾. Cytokines released from tumor cells activate coagulant activity on monocytes, thrombocytes and endothelial cells. Fibrin formation occurs in many types of tumor tissues, and the formation of a fibrin matrix appears to foster tumor growth via the promotion of neoangiogenesis, and by shielding tumor cells against attack from immunocompetent cells⁽⁴⁾. Thrombin also functions as a potent promoter of cancer growth and spread via an increase in tumor cell adhesion and by affecting angiogenesis⁽⁵⁾. Furthermore, the tissue factor is considered to be the primary cancer-related procoagulant, and has been associated with tumor angiogenesis⁽⁶⁾.

D-dimer is a stable end-product of fibrin degradation and levels of D-dimer are elevated by enhanced fibrin formation and fibrinolysis. It is a marker of hypercoagulable stage. D-dimer levels are elevated in the plasma of various solid tumor patients⁽⁷⁾.

The simplicity and specificity of the D-dimer test have led many laboratories to replace less sensitive tests for DIC with D-dimer test, since false positive result may be seen with FDP latex agglutination and D-dimer test is more specific in diagnosis of DIC.⁽⁸⁾ The aim of this study is to identify those patients suffering from solid malignant tumors complicated with intravascular coagulation and fibrinolysis (ICF) by use of D-dimer, and the interrelation of plasma D-dimer level with histologic type of the tumor and metastasis.

Patients and methods

From January to July 2004, a total of 40 patients of with solid malignant tumors were included in this study, there were 26 males and 14 females,

their age ranged from 36 to 73 years for males and from 38 to 70 years for females.

Thirteen of all patients were admitted to Al-Yarmouk Teaching Hospital and the other 27 patients were seen in Hospital of Radiation and Nuclear Medicine clinics.

All patients were proved to have malignancy, and clinical information including full medical and surgical history as well as laboratory data were included from patients' files and formed the basis of this study. All the laboratory tests were done in laboratories of Al-Yarmouk Teaching Hospital.

For the measurement of plasma D-dimer concentration, 3.6 ml of venous blood was collected (from each patient and healthy controls included in this study) into a clean disposable capped plastic tube containing 0.4 ml of 3.8% trisodium citrate in a ratio of 1 volume citrate to 9 volumes of blood. Plasma was obtained by centrifugation of blood at 4000 r.p.m for 15 minutes and kept into plain, disposable, capped, plastic tubes. The plasma levels of D-dimer were measured using a latex agglutination assay, using the commercially available kit diagnostica stag/D-Di test, 92600 Asinieres-sur-serine (France).

The reaction is considered positive when a visible agglutination was detected within 3 minutes, by mixing equal volumes (20 µl was used) of the test plasma and the latex particles suspension against a black background (black test cards were supplied with the kit). Absence of visible agglutination within 3 minutes was considered negative result. Positive and negative results were confirmed by positive and negative control plasma which were supplied with the kit. Positive results were repeated using serial plasma dilutions (1:2, 1:4, 1:8, 1:16, 1:32) until negative result to

determine plasma D-dimer concentration.^(9, 10, 11)

All patients were screened for an "intravascular coagulation and fibrinolysis syndrome" (ICF) using D-dimer test.^(12, 13, 14)

Control group: A total of 15 healthy volunteers, 9 males and 6 females, age and sex matched were included in this study as control group. Plasma D-dimer concentration was tested in all 15 healthy controls.

Statistical analysis was done using SPSS version 10 (statistical package for social sciences). The statistical significance of difference in rate of an outcome between 2 groups was assessed by Fisher's exact significance test. P value of less than 0.05 level of significance was considered statistically significant.

Results

The results presented in this study were based on analysis of 40 patients with malignancy, 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 most frequent histologic types were adenocarcinoma in 29 patients (72.5%), transitional cell carcinoma in 4 patients (10.0 %), undifferentiated small cell carcinoma in 2 patients (5.0%), non -Hodgkin's lymphoma in 2 patients (5.0%), squamous cell carcinoma in 2 patients (5.0%) and large cell carcinoma in 1 patient (2.5%) (Figure 1).

Among the entire series of 40 patients, 22 patients (55%) had metastatic disease and the other 18 patients (45%) were found to have localized tumor.

D-dimer concentration in all healthy controls included in this study was negative (i.e. $<0.5 \mu\text{g/ml}$), and there was a statistically significant difference in the plasma D-dimer concentration between healthy control group and patients with solid malignant tumors (P value = 0.002). (Table 1).

All patients were screened for ICF by the use of plasma D-dimer test. Twenty two patients (55%) out of 40 patients were found to have D-dimer $< 0.5 \mu\text{g/ml}$ (i.e no evidence of ICF syndrome) while 18 (45%) patients out of 40 patients were found to have D-dimer $\geq 0.5 \mu\text{g/ml}$ (evidence of ICF syndrome). (Table 2).

Regarding the histologic type of tumor, rate of positivity of D-dimer was higher with adenocarcinoma (48.2 %) than in other histologic types (36.3%) but the differences failed to reach the level of significance (P value 0.18). (Table 3).

The rate of positivity of D-dimer was higher in cases of tumour with distant metastasis (72.7%) than those without distant metastasis (11.1 %) and the difference was statistically significant (P value ≤ 0.001). (Table 3)

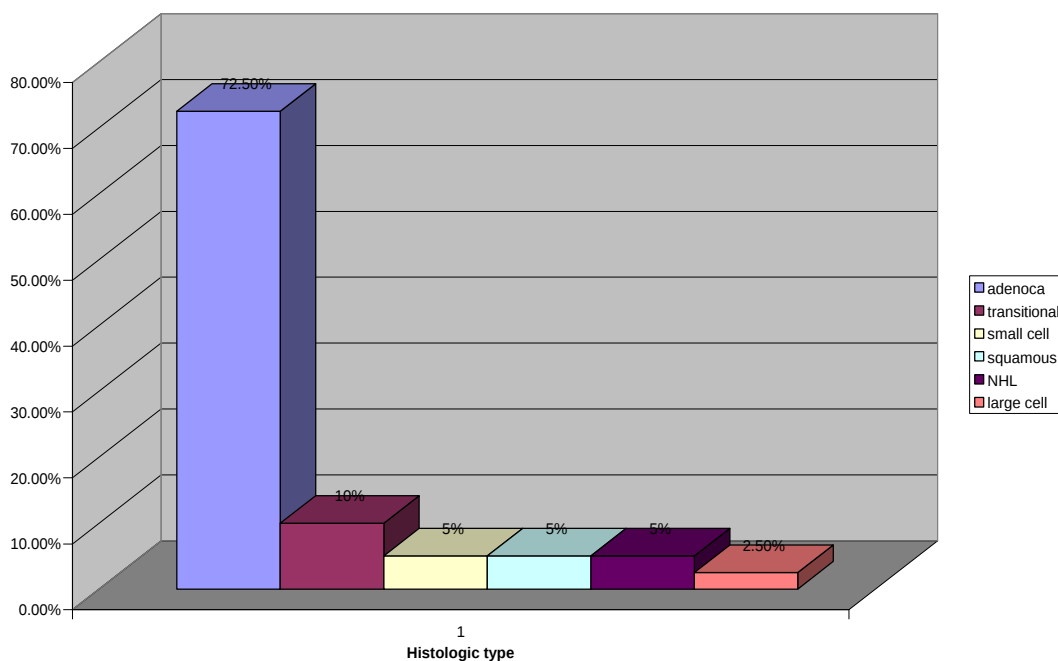


Figure 1: The frequency distribution of cases by histopathologic type of primary tumor.

Table 1: The difference in plasma D-dimer concentration between patients with solid malignant tumors and healthy controls.

	D-dimer conc.(µg/ml)	
	Healthy controls	Patients with solid malignant tumors
Minimum	<0.5	<0.5
Maximum	<0.5	4-8
Median	<0.5	2-4
P value	0.002	

Table 2: Frequency distribution of cases with malignancy by D-dimer concentration.

D-dimer conc. (µg/ml)	No. of cases(percentage)
<0.5	22(55%)
0.5-1	6(15%)
1-2	5(12.5%)
2-4	5(12.5%)
4-8	2(5%)
Total	40(100%)

Table 3: The association between plasma D-dimer concentration with hitologic type of tumor and presence of distant metastasis.

		Positive D-dimer	Total cases with malignancy	P(Fisher's)
		NO(%)	NO(%)	
Distant metastasis	Negative	2(11.1%)	18(45%)	<0.001
	Positive	16(72.7%)	22(55%)	
	Total	18(45%)	40(100%)	
Histologic types	Adenocarcinoma	14(48.2%)	29(72.5%)	0.18[NS]
	Others	4(36.3%)	11(27.5%)	
	Total	18(45%)	40(100%)	

Note: NS = Not Significant

Discussion

Alteration of haemostasis commonly accompanies the progression of malignant diseases and every known component of the haemostatic mechanism may be affected by these disease processes, nearly all patients with an active neoplasm will exhibit at least subtle biochemical change in haemostasis and

few of them clinically develop thrombosis or hemorrhage⁽²⁾.

Plasma levels of D-dimer are elevated in cancer patients. Activation of the extrinsic coagulation system and the fibrinolytic cascade within a tumour is thought to be related with growth, invasion and metastasis^(15, 16). This can explain the significant difference in plasma D-dimer levels

between healthy controls (with negative D-dimer) and patients with solid malignant tumors (with positive D-dimer).

The properties of monoclonal antibody DD/3B6 make the DIMR TEST, a sensitive and simple mean of detecting fibrinolysis associated with intravascular coagulation⁽¹⁷⁾ Therefore, all patients were screened for intravascular coagulation and fibrinolysis and were considered to have evidence of ICF syndrome if their plasma D-dimer level was more than 0.5µg/ml. The frequency of positive D-dimer test in patients with solid malignant tumors was 45% which is lower than the study conducted by Kin HK et al⁽¹⁸⁾ that showed a frequency of 71%, this variation probably can be explained by the differences in type of patients studied, duration of illnesses and extent of the disease.⁽¹⁹⁾

In this study there was a relationship between the histological type of tumors and positivity of D-dimer, the positivity of D-dimer was higher with adenocarcinoma in comparison to other histological types and this may be due to factor X activating procoagulant present in mucin secreted by adenocarcinoma⁽²⁰⁾.

Also there was a relationship between positivity of D-dimer and presence of distant metastasis, the positivity of D-dimer was higher in malignant cases with distant metastasis compared to those without distant metastasis and the difference was statistically significant (P value 0.001). These are consistent with the result of a previous study⁽²¹⁾, which showed that the D-dimer level was higher in patients with metastasis than those without metastasis and the high plasma D-dimer level is indicative of ongoing fibrinolysis within cancer tissue which occurs during tumor progression. 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⁽²²⁾.

Conclusion

Plasma D-dimer test forms a good simple applicable test for assessment of ICF syndrome. Positive D-dimer test is higher in patients with solid malignant tumors compared to normal healthy controls and it is higher in patients with metastatic tumors compared to those with localized tumors and in adenocarcinoma in comparison with other histologic types.

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