Research Article

A study of coagulation profile in neoplastic conditions

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Abstract

Background: Malignant tumors are often associated with thromboembolic episodes and disturbed coagulative processes. Plasma D-dimer and other coagulation parameters form a simple panel of tests for the assessment of the intravascular coagulation and fibrinolysis (ICF) syndrome. The abnormal hemostatic results obtained in a proper clinical setting pave for the suspicion of the ICF syndrome. Moreover, precautionary measures can be taken to avoid its complication by the use of mild anticoagulants.

Objective: To evaluate the changes in hemostatic–clotting parameters in patients with malignancies and elucidate the association of ICF with malignant tumors.

Materials and Methods: This study comprised 60 cases, including apparently normal controls and patients of benign and malignant lesions. After the processing of blood samples, tests such as platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, fibrin degradation products, and D-dimer were done.

Result: A total of 60 cases were evaluated in our study. A strong association was seen between the malignancies and the elevated D-dimer elucidating the presence of ICF in these patients along with other altered coagulation parameters in comparison with apparently normal controls in the study.

Conclusion: Increased D-dimer and altered coagulation parameters significantly correlate with malignant behavior of tumors and their spread. They might be useful indicators of aggressive tumor biology and behavior.

KEY WORDS: D-dimer, malignancy, coagulation

Introduction

According to Armand Trousseau, "if the diagnosis of a suspected carcinoma of an internal organ could not be verified, spontaneous appearance of thrombophlebitis afforded necessary proof for diagnosis" and described "phlegmasia alba dolens" as a presenting symptom of occult cancer.[1]

Malignancies show an increased susceptibility to thromboembolic events when compared with benign tumors and the general population. Ovarian, pancreatic, prostatic, and lung cancers and mucin-producing carcinomas of gastrointestinal tract are among the malignancies often associated with thromboembolic episodes.[2]

Thrombosis occurs spontaneously, after surgery, radiation therapy, and anticancer treatment and might be the first manifestation of underlying cancer.[3]

In this study, changes in hemostatic parameters and their relation to cancer are analyzed.

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Materials and Methods

This study was conducted during a period of 6 months from August 2013 to January 2014. A total of 60 cases were included in this study, including apparently normal controls and patients with benign and malignant tumors; all the patients were admitted to New Civil Hospital, Surat, Gujarat, India.

After taking consent, complete history and clinical findings with details regarding the tumor nature and laboratory data were collected.

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For the evaluation of hematological parameters, 2 mL blood sample was collected in EDTA Vacuette and run on Sysmex Kx 21 for the evaluation of Hb, total count, and platelets.

For coagulation parameters, 2 mL blood sample was collected in the Citrate Vacuette. Plasma thus isolated was evaluated for prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), fibrin degradation products (FDP), and D-dimer.

- Platelet-poor plasma was prepared from citrated samples immediately after venipuncture by centrifugation for 10 min at 1,500 rpm at room temperature.
- Plasma was transferred to plastic tubes, frozen, and stored at –40°C until evaluated.
- Evaluation was done on fully auto coagulometer (Stago STA compact CT coagulation analyzer).
- FDP was performed using latex agglutination test kit (TULIP XL FDP).
- D-dimer levels were measured by a quantitative latex assay (STA-LIA test D-DI).
- Pooled plasma from healthy individuals were prepared and divided into aliquots, each containing 1 mL, and stored at –40ºC to be used simultaneously with patients' plasma. Positive and negative control plasma samples (for D-dimer test) were supplied with plasma D-dimer kit.
- all the laboratory tests were performed in the laboratory of the hospital.

The reference ranges were established by our laboratory, which is NABL accredited. The reference ranges were:

- Platelet count: 150,000–400,000/mm^3
- PT = 11–15 s
- APTT = 29–35 s,
- fibrinogen = 250–450 mg/dL,
- Plasma D-dimer concentration < 0.5µg/mL.
- FDP, being a qualitative test, gives result as either positive or negative.

The concept of "intravascular coagulation and fibrinolysis (ICF) syndrome" was introduced by Owen and Bowie, and the purpose was to examine the incidence and type of hemostatic derangement in patients with malignancies.[4]

Patients were considered to have ICF if their D-dimer was more than 0.5 µg/dL.

The concept of ICF of Owen and Bowie was adopted and their classification of overcompensated, compensated, and decompensated ICF was tested with an attempt to identify key tests that might help to ascertain patients with coagulation problems.

The D-dimer and platelets were used as indicators and to separate 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); and
4. those with decompensated ICF (elevated D-dimer and decreased platelets count)[2].

This has been correlated with acute, subacute, and chronic disseminated intravascular coagulation (DIC) and decompensated, overcompensated, and compensated DIC, respectively.

- A set of hemostatic tests were applied to these four groups, and many tests were done. (PT, APTT, fibrinogen, and D-dimer).
- In this study, D-dimer test has been considered for the diagnosis of ICF, because it is presently regarded to be more specific for fibrin degradation products, while the formation of FDP, X, Y, D, and E fragments, may be either fibrinogen or fibrin derived following the plasmin digestion.[5,6]

Statistical Analysis

Data were entered into a computerized database for statistical analysis. The mean, standard deviation, standard error of mean, standard error of difference, *t*-value, and 95% confidence intervals of various variables were calculated. The statistical significance of difference in the rate of an outcome between the two groups was assessed by χ^2-test.

Result

In our study, 37.14% of malignancies showed thrombocytosis, indicating slight tendency toward thrombocytosis (*n* = 13/16) [Table 1].

Benign lesions showed PT from 11 to15 s (85.71%). Malignancies predominantly showed APTT > 35 s (85.71%) [Table 2].

Benign lesions showed APTT from 29 to 35 s (92.86%). Malignancies predominantly showed APTT > 35 s (85.71%). Thus malignancies exhibited elevated PT and APTT when compared with control group and benign lesions.

In our study, control group and patients with benign lesions showed exclusively to have fibrinogen from 250 to 450 mg/dL (100%). Patients with malignancies predominantly showed fibrinogen within 250 and 450 mg/dL (45.71%). However, hypofibrinogenemia (17.14%) and hyperfibrinogenemia (37.14%) were seen only in patients with malignancies. Malignancies tended to show abnormal fibrinogen (54.29%) when compared with benign lesions [Table 3].

In our study, control group and benign lesions showed negative FDP test (100%). Malignancies predominantly revealed positive FDP test (80%). Malignancies tended to show a positive FDP test when compared with control group and benign lesions [Table 4].

In our study, control group and patients with benign lesions showed D-dimer between 0.2 and 0.5 μg/mL (100% and 92.86%, respectively). Patients with malignancies predominantly showed D-dimer > 0.5μg/mL (88.57%). Such patients with elevated D-dimer are said to have ICF syndrome.

Malignancies tended to show elevated D-dimer when compared with benign lesions.

A singular case of elevated D-dimer in benign lesions was of recently operated intestinal polyp explaining the elevated D-dimer in this case [Table 5].

Table 1: Distribution according to the platelet count

Platelet count, ×10³/mm³	Number of cases			
	Normal, *N* (%)	Benign, *N* (%)	Malignant, *N* (%)	Total (%)
<150	2 (18.18)	3 (21.43)	2 (5.71)	7 (11.67)
150–400	8 (72.73)	9 (64.29)	20 (57.14)	37 (61.67)
>400	1 (9.09)	2 (14.29)	13 (37.14)	16 (26.67)
Total	11 (100)	14 (100)	35 (100)	60 (100)

Table 2: Distribution according to the PT

PT (s)	Number of cases			
	Normal, *N* (%)	Benign, *N* (%)	Malignant, *N* (%)	Total (%)
11–15	10 (90.91)	12 (85.71)	8 (22.86)	30 (50)
>15	1 (9.09)	2 (14.29)	27 (77.14)	30 (50)
Total	11 (100)	14 (100)	35 (100)	60 (100)

Table 3: Distribution according to FIB

FIB, mg/dL	Number of cases			
	Normal, *N* (%)	Benign, *N* (%)	Malignant, *N* (%)	Total (%)
<250	0 (0)	0 (0)	6 (17.14)	6 (10)
250–450	11 (100)	14 (100)	16 (45.71)	41 (68.33)
>450	0 (0)	0 (0)	13 (37.14)	13 (21.67)
Total	11 (100)	14 (100)	35 (100)	60 (100)

Table 4: Distribution according to FDP

FDP	Number of cases			
	Normal, *N* (%)	Benign, *N* (%)	Malignant, *N* (%)	Total (%)
Positive	0 (0)	0 (0)	28 (80)	28 (46.67)
Negative	11 (100)	14 (100)	7 (20)	32 (53.33)
Total	11 (100)	14 (100)	35 (100)	60 (100)

Table 5: Distribution according to D-dimer

D-dimer, μg/mL	Number of cases			
	Normal, *N* (%)	Benign, *N* (%)	Malignant, *N* (%)	Total (%)
0.2–0.5	11 (100)	13 (92.86)	4 (11.43)	28 (46.66)
>0.5 (ICF)	0 (0)	1 (7.14)	31 (88.57)	32 (53.33)
Total	11 (100)	14 (100)	35 (100)	60 (100)

Table 6: Distribution of the ICF syndrome cases into decompensated, compensated, and overcompensated

Platelets (×10³/mm³)	Number of cases		
	Benign, *N* (%)	Malignant, *N* (%)	Total (%)
150–400 (compensated)	1 (5)	199 (95)	20 (62.50)
<150 (decompensated)	0 (0)	2 (100)	2 (6.25)
>400 (overcompensated)	0 (0)	10 (100)	10 (31.25)
Total	1	31	32 (100)

Table 7: Lymph node involvement status

Lymph nodes	No. of cases	Mean D-dimer (µg/mL)
Involved	12	2.325
Not involved	7	1.85
Total	19	100

Table 8: Statistical comparison between apparently normal controls and patients with malignancies

Variables	Malignancy			Normal			*t*	df	95%CI		SED	*P*
	Mean	SD	SEM	Mean	SD	SEM			LL	UL		
PLT	334.14	104.56	17.67	273.73	126.52	38.15	1.5899	44	–16.17	137	38.001	0.119
PT	23.151	17.48	2.955	13.691	0.887	0.267	1.7805	44	–1.248	20.169	5.313	0.0819
APTT	46.426	18.796	3.177	32.945	2.25	0.678	2.3553	44	1.946	25.015	5.723	0.023
FIB	409.51	163.44	27.63	341.18	66.43	20.03	1.3437	44	–34.16	170.8	50.855	0.1859
D-dimer	2.7246	2.9599	0.5003	0.3682	0.061	0.0184	2.6199	44	0.5437	4.169	0.899	0.012

Table 9: FDP status

FDP	Normal controls	Malignant
Positive	0	28
Negative	11	7
Total	11	35

ICF syndrome is classified into compensated, decompensated, and overcompensated types based on low, adequate, and high platelet levels of the patient, respectively. In our study, the majority of patients with malignant lesions with elevated D-dimer showed compensated type of ICF (61.29%), followed by overcompensated type (32.26%) and decompensated type (6.45%) [Table 6].

In our study, the status of lymph node involvement in 19 patients with malignancies was available. Of the 19 cases, 12 showed tumor involvement while seven of them did not. The mean D-dimers were 2.325µg/mL and 1.85µg/mL, respectively [Table 7].

Statistical tests were done.The mean, standard deviation (SD), and standard error of mean (SEM) for various variables were calculated in the normal and malignancies groups. Statistical comparison was done between the normal group and malignancies group. The *t* value, degree of freedom (*df*), 95% confidence interval (CI), standard error of difference (SED), and *P* value were calculated for each of the variables.

P value of < 0.05 was considered to be statistically significant. [Table 8].

The χ^2-test was done for FDP, thus comparing the malignancies vs. normal controls group and malignant vs. benign lesions group [Table 9].

The *P* values for the above-mentioned comparison is <0.0001, which is extremely statistically significant.

Discussion

Cancer is a prothrombotic state. Experimental and clinical studies have shown an association between cancer and haemostasis, which is altered and provides a growth benefit to tumors, although clinical symptoms occur less often.[7] The tumors, through the production of procoagulant factors, and the host, through its inflammatory response, participate in the process.

Abnormal coagulation activation encourages endothelial adhesion, metastatic spread, tumor cell growth, and survival.[2]

In this study we studied the hemostatic and coagulation profile in 60 cases (35 showed malignancies, 14 showed benign lesions, and 11 were apparently normal controls). Complete blood count, PT, APTT, Fibrinogen, D-Dimer, and FDP were done.

Amin et al.[7] showed that the percentage of patients with abnormal coagulation was 88%. Mohammed et al.[2] showed that the coagulation abnormalities were in 80% patients. In our study, 94.28% malignancies showed coagulation abnormalities comparable with the above studies.

Advanced cancer shows increased platelet activation, indicated by increased platelet turnover and decreased platelet survival time.[8]

Mohammed et al.[2] showed that mean platelet count in cancer was 317.8 ± 23.46 ×10^3/cm and in control group was 260.7 ± 7.96 ×10^3/cm. Amin et al.[7] showed that the mean platelet count = 286 ± 144 × 10^3/cm in malignancies in comparison with the control group (212 ± 46 × 10^3/cm). However, Omer and Abdalla[9] showed the mean platelet count in cancer was 249.6 ± 142.3 × 10^3/cm, while for the control group, it was 279.7 ± 77.9 × 10^3/cm. Suega and Bakta[10] showed the mean platelet = 365 × 10^3/cm in malignancies.

In our study, the mean platelet count in malignancies was 334.14 ± 104.56 × 10^3/cm, which was higher when compared with apparently normal controls (273.73 ± 126.52 × 10^3/cm).

Mohammed et al.[2] showed that mean PT in cancer was 15 ± 0.32 s and in control group was 12.9 ± 0.27 s. Amin et al.[7] showed that the mean PT was15 ± 3s in malignancies group when compared with the control group with a mean PT of 13 ± 1 s. Omer and Abdalla[9] showed that the mean PT in cancer was 13.7 ± 1.3 s, while in control group, it was 12.2 ± 0.8 s.

In our study, the mean PT in malignancies was 23.15 ± 17.48 s, higher in comparison with the patients with benign lesions and apparently normal controls (14.28 ± 1.91 s and 13.69 ± 0.89 s, respectively).

Mohammed et al.[2] showed that mean APTT in cancer was 37.9 ± 0.31 s and in control group was 35.1 ± 0.56 s. Omer and Abdalla[9] showed that the mean APTT in cancer was 35.7 ± 6.6 s and in the control group was 29.6 ± 2.2 s.

In our study, the mean APTT in malignancies was 46.43 ± 18.8 s, higher in comparison with benign lesions and apparently normal controls (33.66 ± 4.26 s and 32.95 ± 2.25 s, respectively).

In our study, there is a significant difference in the mean APTT values of the control group and patients with malignancies, the difference being statistically significant ($p = 0.023$).

Mohammed et al.[2] showed that the mean fibrinogen in cancer was 310 ± 15 mg/L and in control group was 300 ± 8 mg/dL. Amin et al.[7] showed that the mean fibrinogen was 300 ± 100 mg/dL in malignancies in comparison with the control group (230 ± 60 mg/dL).

In our study, the mean fibrinogen in malignancies was 409.51 ± 163.44 mg/dL, higher in comparison with benign lesions and apparently normal controls (346 ± 57.94 mg/dL and 341.18 ± 66.43 mg/dL, respectively).

As the half-life of fibrinogen is 4 days, a 50% or greater decrease in fibrinogen over 1 day is convincing evidence of DIC or fibrinolysis, despite the final value being within normal range.[2]

D-dimer, the main breakdown fragment of fibrin, is a biochemical marker of thrombogenesis and fibrin turnover. High D-dimer is an indirect marker of hypercoagulation activation and thrombolysis. Procoagulant factors in cancer cause constitutive activation of the coagulation cascade leading to thrombin and fibrin generation. Fibrin formation and remodeling process provides extra cellular matrix essential for the initial step of cancer cell to migrate, invade, and metastasize. It is summarized that more advanced the cancer, more D-dimer is produced as an marker for coagulation activation.[10]

Amin et al.[7] showed the mean D-dimer was 3.708 ± 3.236 µg/mL in malignancies in comparison with the control group (0.325 ± 0.365 µg/mL). Omer and Abdalla[9] showed the mean D-dimer in cancer was 2.19632 ± 2.11095 µg/mL, while for the control group mean D-dimer was 0.21365 ± 0.10357 µg/mL. Mohammed et al.[2] showed D-dimer in cancer was 2–4 µg/mL and in control group was <0.5 µg/mL. Suega and Bakta[10] showed the mean D-dimer was 1.260 µg/mL in malignancies.

In our study, a statistically significant difference in the mean D-dimer of patients with malignancies and the control group is seen ($p = 0.012$).

However, high D-dimer can be seen in DIC, vaso-occlusive crisis in sickle cell disease, thromboembolic events, myocardial infarction, surgery, inflammatory processes, smoking, senility, pregnancy, trauma, and infection.

Plasma D-dimer correlates with tumor burden, no. of metastatic sites, progression kinetics, cytokines related to angiogenesis,[11] invasion depth, lymph node metastasis, peritoneal dissemination, distant metastasis, tumor size, and TNM stage.[12] The D-dimer and platelets were used as markers to separate the patients into four groups of ICF.[5,13]

Patients with no ICF, those with overcompensated, compensated, and decompensated ICF.

Mohammed et al.[2] showed that the patients with ICF was 45% (n = 18/40). Those with overcompensated ICF was 38.88% (n = 7/18), with compensated ICF was 38.88% (n = 7/18), and with decompensated ICF was 22.22% (n = 4/18).

In our study, patients with malignancies showing ICF was 88.57% (n = 31/35). Those with overcompensated ICF was 32.26% (n = 10/31), with compensated ICF was 61.29% (n= 19/31), and with decompensated ICF was 6.45% (n = 2/31).

This variation is probably owing to the difference in the type of patients that were studied in the two studies. The percentage of patients with compensated ICF is comparable in both the studies.

Suega and Bakta[10] found patients with ICF was 75.94% (n = 60/79), patients with overcompensated ICF was 40% (n = 24/60), which is comparable with our study. Omer and Abdalla[9] found ICF in 88% patients (n = 53/60). In this study most of the patients (87%) had normal platelets counts, 10% had thrombocytopenia and 3% had an elevated count suggesting a compensated ICF in majority of the patients which is also comparable to our study.

Advance cancer stage with high tumour load and elevated proliferation rate is associated with high coagulation activation, its duration and severity.

Blackwell et al.[14] showed 75.75% (n = 25/33) of patients with involved lymph nodes had elevated D dimer, which is comparable with our study. In our study patients of malignancies with lymph node involvement showed elevated D- dimer (83.33%, n = 10/12).

In our study, there were 19 patients with malignancies in which the status of lymph node involvement was available. Of the 19 cases, 12 showed tumor involvement in lymph nodes, while 7 were negative. The mean D-dimers was 2.325 ± 3.33 µg/mL and 1.85 ± 3.33 µg/mL, respectively, which showed a significant difference.

Given its sensitivity for predicting positive lymph node involvement, a role of D-dimer, along with other predictive factors to decide whether or not axillary lymph node dissection is needed may be used.[14]

The χ^2-test was applied on the FDP values, thus comparing malignant lesions vs. normal controls group.

The *P* value for the above comparison is <0.0001, which is extremely statistically significant.

Conclusion

Malignant cells can interact with the haemostatic system in several ways, but the two major interactions are the capacity to produce and release procoagulant, fibrinolytic activities, and inflammatory cytokines; and direct interaction with other blood cells (i.e., endothelial cells, platelets, and monocytes).

Abnormal coagulation activation encourages endothelial adhesion and metastatic spread, tumor cell growth, and their survival. Despite the well-established link between cancer and venous thrombosis, anticoagulation is not the standard treatment for these patients. Assessment of the coagulation profile in cancer might help understanding their relationship with coagulation abnormalities and in the prediction as well as management of complications arising from them. Disruption of blood coagulation impairs metastasis. Use of mild anticoagulants in the setting of cancer with DIC might be considered hoping that antithrombotic treatment may have a positive result on tumor growth and propagation.

Our study implies a relation between activation of hemostasis mirrored by elevated D-dimer and malignancy. D-dimer might be used as a universal surrogate indicator of the relation between cancer and the activation of hemostasis and fibrinolysis, with elevated D-dimer levels symbolizing the pathogenesis of a more aggressive malignant process associated with poor clinical results.

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