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Pathology

Coagulation Profile in Non-Haematological Malignancies

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Abstract **Original Research Article**

A variety of Coagulation abnormalities have been reported in patients with malignant lesions especially in the form of Thromboembolic phenomena. These can be detected with simple and inexpensive tests and can help prevent complications. The aim of the present study is to evaluate the coagulation profile in patients with non-Haematological malignancies with respect to the changes in Prothrombin Time (PT), activated Partial. Thromboplastin Time (aPTT) and fibrinogen levels to elucidate any prognostic significance of haemostatic abnormalities in non-haematological malignancies. A total of 70 cases of non-haematological malignancies were evaluated for changes in PT, aPTT and fibrinogen levels and compared to the normal control values. Significant higher levels of Fibrinogen levels were observed in patient group values when compared to normal control values.

Keywords: Coagulation, Pt, aPTT, Fibrinogen, Malignancies.

INTRODUCTION

Malignant neoplasms are known to occur in people of all age groups with an increasing incidence noted in elderly age group [1]. Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 [1].

A wide range of coagulation changes occur in malignant diseases & can predispose to thromboembolic phenomena or haemorrhage [2].

Such thromboembolic phenomena are more common in Solid organ malignancies like Lung, ovaries, Pancreas, mucin producing GI tumours [3].

Abnormalities of the so-called "routine" blood coagulation tests have been described in up to 92% of cancer patients [4]. The abnormalities can include DIC, altered platelet function, Thrombocytosis/ thrombocythemia, circulating Pro coagulants/ inhibitors [5].

The aim of the present study is to evaluate the coagulation profile in patients with non-Haematological malignancies with respect to the changes in Prothrombin Time(PT), activated Partial Thromboplastin Time (aPTT) and fibrinogen levels and known their relevance in prognosis or treatment.

MATERIAL AND METHODS

This is a prospective study undertaken on patients attending the Inpatient & outpatient clinics in Osmania General Hospital & MNJ Institute of oncology & research, Hyderabad from November 2009 to April 2010.

Newly diagnosed cases of Non Haematlogical malignancy without prior chemotherapy or radiotherapy were included in the study.

Patients with previous history of bleeding diathesis or liver diseases or any other chronic medical illness or using Oral contraceptive pills or medication such as Antiplatelets drugs or Aspirin or history of recent transfusion were excluded from the study.

Cytological & Histopathological, Radiological details were obtained in each case and the TNM stage was determined as per WHO/ AJCC classification (2008). Consent for study was obtained from all the patients.

Twenty subjects who were apparently healthy & normotensive, without any history of drug intake (including Oral Contraceptives), bleeding disorders, and liver diseases were included as controls.

For evaluation of coagulation parameters blood was withdrawn slowly from an antecubital vein using 20 guage needle and 5ml disposable syringe under aseptic conditions and transferred into EDTA vacutainers (2ml for platelet count) and Citrate vacutainers (2ml 3.8%Na.Citrate).Platelet poor plasma (PPP) was prepared from citrated blood immediately by centrifuging blood at 1500-2000rpm for 15 min and processed immediately or stored at -20^{0}C till further processing. Platelet count was estimated on a sysmex three part analyser (XP 300) and values were recorded. Slide method for estimation of platelets was done when there was flag shown in the hematology analyser. PT, aPTT and Fibronogen assay were performed on an MC Plus 1000 Coagulomter (Tulip diagnostics) using reagents from Tulip diagnostics as per manufacturer's guidelines.

In this study, a total of 90 cases (70 patients & 20 controls) were analysed for coagulation profile (Platelet count, PT, aPTT, Fibrinogen levels).

RESULTS

Table-1: Age distribution of study & Control group.

Age Group in years	No. of cases(study) Total :70	No of cases(Control) Total :20
30-40	12	04
41-50	14	08
51-60	15	03
61-70	20	04
> 70	09	01

Table-2: sex distribution

Group	Males	Females
Study (70)	24	46
Control (20)	10	10

Male: female ratio is 0.5:1

Table-3: site of distribution

Site of the tumour	No of cases
Breast	23
Ovary	7
Gastric	9
Pancreas	5
Colon/Rectum	6
Lung	8
Cervix	3
Miscellaneous	9
Total	**70**

Table-4: PT, apt t, Fibrinogen and Platelet count values in 70 cases recorded

S.no.	Age/sex	TNM Stage	P.T(sec)	aPTT (sec)	Fibrinogen (mg/dl)	Platelet count(/cu.mm)
1	55y/F	IV	11.5	26.9	620	650000
2	55/F	II	16.5	25.2	400	250000
3	36/F	IV	11.9	22.4	650	502000
4	55/F	I	12.1	38.4	520	300000
5	50/F	I	14.1	28.9	300	670000
6	65/F	IV	13	24.8	620	358000
7	45/F	IV	14.3	29.6	680	480000
8	43/F	III	13	29.4	460	760000
9	46/F	III	13.9	23.5	340	250000
10	63/F	I	10.9	24	280	450000
11	35/F	II	11.6	23	380	350000
12	36/F	II	11.3	29.9	440	345000
13	48/F	III	12.2	21.5	450	237000
14	38/F	IV	13.1	25.1	530	185000
15	62/F	IV	12.2	22.5	440	287900

16	50/F	III	11	21.2	260	178900
17	65/F	IV	11.8	28.3	530	345900
18	65/F	III	11.6	18.3	538	234500
19	75/F	II	11.5	27.4	430	167800
20	65/F	III	11.9	22	373	210000
21	36/F	II	11.2	20	392	319000
22	45/F	IV	13.9	40.3	490	485000
23	35/F	III	12.5	27.4	408	415000
24	40/F	III	9.3	26.9	330	540000
25	60/F	I	14.4	27.6	360	320000
26	70/F	III	11.9	22	373	470000
27	50/F	I	12.4	16	320	185000
28	65/F	IV	12	27	550	765000
29	40/F	III	11.8	27.3	480	340000
30	48/F	II	12	27	550	243000
31	60/M	II	11.3	17.4	352	153000
32	40/M	III	18	45	438	465000
33	65/M	III	11.9	30.3	460	265000
34	65/M	III	12.5	28.6	380	241000
35	50/M	III	13.1	38.4	480	196000
36	66/M	IV	12.2	24.5	380	138000
37	60/M	III	12.2	31	480	525000
38	52/F	III	12.5	28.6	380	415000
39	30/F	II	11.3	17.4	352	265000
40	35/F	III	20	48	590	225000
41	55/M	II	10.5	19.6	350	185000
42	56/M	II	15	29.2	500	265000
43	54/F	II	12.5	20.1	450	325000
44	55/F	I	11.9	17.2	400	195000
45	65/M	III	11.3	35.9	441	235000
46	65/F	III	12	21.3	440	285000
47	55/M	III	11	34.5	375	260000
48	60/M	III	11.3	24.2	380	320000
49	50/F	III	12.2	18.7	480	185000
50	35/M	III	11.6	24.1	310	225000
51	58/M	IV	12.8	29.4	397	525000
52	65/M	III	12.3	25	375	485000
53	65/F	III	12.2	21.5	380	265000
54	60/M	IV	11.3	25.5	410	305000
55	58/M	III	12.6	30.1	395	295000
56	45/M	IV	13.4	34.5	390	650000
57	80/M	III	12.8	29.3	388	235000
58	48/M	III	13.5	30.3	360	187000
59	60/F	II	11.4	19.1	331	225000
60	38/F	I	11.9	30.4	300	185000
61	48/F	II	13	39	340	265000
62	60/F	III	11.1	28	310	258000
63	55/M	IV	12.3	25	580	458000
64	60/M	II	12.3	22.3	400	325000
65	65/F	II	11.4	25	391	341000
66	47/F	III	47.6	67.7	600	168000
67	37/M	II	12.4	30.2	410	248000
68	39/M	II	10.5	26.1	270	269000
69	46/F	II	12.3	34	350	155000
70	55/F	II	12	24.2	310	201000

Table-5: coagulation profile in control group

SNO	AGE/SEX	PT(sec)	aPTT(sec)	Fibrinogen (mg/dl)	Plate count (/ Cumm)
1	32/M	11.4	22.5	296	252000
2	33/M	11.3	23.1	298	185000
3	33/F	10.9	24.1	292	285000
4	39/M	11.1	24.5	295	225000
5	40/M	11.1	23.5	290	352000
6	42/F	11.5	23.5	294	196000
7	43/F	10.8	22.1	296	325000
8	45/F	11	22.5	300	248000
9	45/F	12	24	310	312000
10	45/M	12.8	23.5	305	167000
11	45/M	11	23.9	300	400000
12	47/F	10.9	24	294	285000
13	50/F	11.5	24.5	292	325000
14	55/M	11.3	23.5	298	165000
15	59/F	11.2	22.9	290	187000
16	61/M	11.3	24.1	300	258000
17	62/M	10.8	26	304	450000
18	67/M	11.4	24.5	298	210000
19	66/M	11.5	23.5	296	169000
20	78/F	11.5	24	290	198000
Mean+/_2SD		10.9-11.7	22.3-25.1	244-350	151000-313000

Table-6: p value for fibrinogen estimation using student t test

	CASES	***CONTROLS***	
Mean	422.8428571	296.9	
Variance	9039.235818	28.09474	
Observations	70	20	
Hypothesized Mean Difference	0		
df	70		
t Stat	11.02318928		
P(T<=t) one-tail	**2.97758E-17**		**Significant**
t Critical one-tail	2.38080746		
P(T<=t) two-tail	**5.95517E-17**		
t Critical two-tail	2.647904603		

OBSERVATIONS

In the present study,47 cases (67.1%) had values of PT more than the control range(11.1-11.5 sec) and 38 cases (54%) had aPTT values more than the control range (22.3-25.1 sec) and 18 cases (25%) had platelet count over and above the normal range.

But significant elevations were observed in fibrinogen levels with highest levels being recorded in stage IV, indicating a correlation between disease stage and fibrinogen levels.

In our study 23 cases of carcinoma breast (which constituted the major malignant group), had a mean fibrinogen value of 458mg/dl and 20 out of 23 cases(87%) had fibrinogen levels more than 2 SD the control population. The fibrinogen levels were highest in stage IV with 8 /23 (34.78%) cases having values between 440-650mg/dl with a mean of 590 mg/dl which is 60 % higher than the control mean. From the table 6 it is clear that fibrinogen levels have significant p value in malignancies.

DISCUSSION

Haematological alterations are known to occur in neoplastic diseases. Thrombosis is a common complication of malignant disease and pulmonary embolism is the second most common cause of death in cancer patients [6]. The most important point in the relationship between malignancy and coagulation disorder is fibrinogen. Studies on the association between tumour cells and procoagulants and fibrinolytic factors have strongly suggested that local thrombin and plasmin generation may be important in tumour progression [6, 7]. Given that one target for both these serine proteases is fibrinogen, a logical extension of this hypothesis is that local fibrin deposition and dissolution may be key determinants of tumour growth and/or dissemination [7].

Patel *et al*. [8] in their study showed that around 27% of malignant lesions have PT values more than 15 sec and aptt values >35sec and fibrinogen levels > 450mg/dl (45%) as compared to the benign lesions, thus reemphasising the fact that malignant lesions and Coagulation abnormalities go hand in hand.

Similarly Mohhamed *et al*. [9] and Amin *et al*. [10] Showed 80 % and 88% of patients in their study demonstrate coagulation abnormalities respectively which is comparable to our study which showed 87% cases had Coagulation abnormalities.

The mean platelet count in our study for patient group is 324.38+/-147.94X10^3 which is comparable to Patel *et al*. who demonstrated 334.14+/-104.56X10^3. PT values in malignancies in study by Amin et al was 15+/-3 secs when compared to control group of 13.7+/-1.3sec and Patel *et al*. showed mean PT values of 23.15 sec in Malignancy cases. In our study the mean PT value was 12.91 +/ 8.9 and that of Normal control value of 11.31+/-0.9 sec.

Similarly with APTT, Omer and Abdalla [11] showed values of 35.7+/-6.6s and control group 29.6+/-2.2 secand patel *et al*. demonstrated values of 46.43+/-1.8 sec which is higher than the normal control group of 32.95+/-2.25sec.

In our study the mean APTT levels are 27. 49+/- 16.4 sec and the control values are 23.71+/-1.74, thus comparable to the previously published studies.

Amin *et al*. showed Fibrinogen levels values of 300+/-100 mg/dl and control values of 230+/-60mg/ dl and Patel *et al*. showed fibrinogen values of 409.51+/-163.44 mg/dland Normal controls of 341.18+/-66.43 mg/dl.

In our study fibrinogen mean values were 422.84+/-190.14 mg/dl and control group was 296.9+/-10.6 mg/dl and the values are statistically significant as demonstrated by the student T test (table above). The above findings demonstrate that fibrinogen levels may act as markers for poor outcome in malignancies.

CONCLUSION

Malignant cells are known to interact with hematopoietic system either by producing procoagulant factors or fibrinolysis or other cytokines [8]. The coagulation system on the other hand helps tumour cells to metastasize by forming fibrin deposits on the stromal endothelial cells thus paving way for their spread. Though trousseau syndrome (venous thromboembolism) has known to be occurring in malignancies, coagulation profile is not a common investigation ordered. Studying coagulation abnormalities might help in assessing the prognosis of the malignant disease. Early diagnosis of the coagulation abnormalities and intervention help prevent certain complications associated with it like DIC.

In the present study, we were able to demonstrate a relationship between elevated fibrinogen levels and advanced stage of disease, thus indicating an activation of coagulation pathways in patients with poor outcomes.

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