Abstract

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/thrombocytethemia, 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 Haematological 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°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 Coagulometer (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) | No of cases (Control) |
|--------------------|----------------------|-----------------------|
| 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 |

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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 |
| Variance | 9039.235818 |
| Observations | 70 |
| Hypothesized Mean Difference | 0 |
| df | 70 |
| t Stat | 11.02318928 |
| p(T<=t) one-tail | 2.97758E-17 |
| 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 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 > 35 sec and fibrinogen levels > 450 mg/dl (45%) as compared to the benign lesions, thus reemphasising the fact that malignant lesions and Coagulation abnormalities go hand in hand.

Similarly, Mohamed 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+/-1.3 sec 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 sec and that of Normal control value of 11.31 +/- 0.9 sec.

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

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+/-60 mg/dl and Patel et al. showed fibrinogen values of 409.51+/-163.44 mg/dl and 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 trosseau 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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