# COAGULATION PROFILE IN PATIENTS PRESENTING WITH MALIGNANCIES WITH SPECIAL REFERENCES TO HEAD AND NECK EPITHELIAL CANCERS, LEUKAEMIAS AND LYMPHOMAS

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**ABSTRACT**

**BACKGROUND**

Cancer can cause activation of coagulation in many ways and there is definite evidence of abnormalities in haemostatic mechanism which is seen by the presence of one or more circulating markers of haemostatic activation & this is found to be potentiated by the release of tissue factors or procoagulants from normal tissue destructions during tumour development.

**OBJECTIVES**

To evaluate the range of different types of haemostatic abnormalities in haematological and epithelial malignancies, especially the head and neck epithelial malignancies.
To look for the differences in the grades of these abnormalities in metastatic & non-metastatic malignancies.
To understand the prognostic value of routine tests of coagulation while predicting the outcome of the patient.

**MATERIALS AND METHODS**

The study was conducted in the Department of Pathology, Gauhati Medical College & Hospital, Guwahati from July 2004 to June 2005. 70 cases comprising of head and neck epithelial malignancies, leukaemias and lymphomas without clinical presentation of haemorrhage or thrombosis were selected and coagulation profiles were seen.

**RESULTS AND OBSERVATION**

Out of 70 cases of both sexes & different age groups prior to therapeutic intervention, metastatic cases were 22, non-metastatic cases were 29, and 19 cases belonged to leukaemias and lymphomas. The commonest age group affected was 51–60 yrs. and male: female was 3.7: 1. The most frequent abnormality was 41 cases (58.57%) of FDP positivity in the serum followed by 36 cases (51.43%) of hyperfibrinogenaemia; 32 cases (45.71%) shortened bleeding time, etc.

**DISCUSSION**

Activated coagulation in cancer leads to increased fibrin deposition stimulated by the destroyed tissues; increased FDPs being a strong marker of coagulation and fibrinolytic activation; increased platelet aggregation by the micro vesicles shed by tumour cells; prolonged PT & APTT being well known markers for disseminated intravascular coagulation(DIC). The abnormalities were more pronounced in the metastatic cases.

**CONCLUSION**

We can conclude that various haemostatic abnormalities explaining the disturbed haemostatic-fibrinolytic balance are frequently associated with malignant diseases giving an impetus for development of various researches, prophylactic and therapeutic approaches.

**KEYWORDS**

Haemostatic; Procoagulant; Hyperfibrinogenaemia; Disseminated; Malignancy.

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**INTRODUCTION:** The association of haemostatic abnormalities with malignant diseases and their clinical significance has been a subject of intense scrutiny and research. Strong evidences are available that interactions between tumour cells & host tissue components like vascular endothelium, monocyte-macrophage, platelet and various factors of coagulation pathway lead to a 'hypercoagulable' state in patients with cancer. The clotting- fibrinolytic system is involved in various manifestations of cancer & in the pathogenesis of malignancy, tumour cell growth & dissemination.[1] The clinical and laboratory features of this association depend upon the degree of balance between the coagulation system and the fibrinolytic system, the latter being activated by the formation of intravascular thrombi as a result of activation of the former.[2]

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The importance of this relationship between malignancy and the haemostatic system is seen first, by the demonstration of fibrin deposits in and around tumours leading to our assumption that blood coagulation plays an important role in growth, invasion and metastasis of the tumour and secondly the thromboembolic and haemostatic manifestations of coagulation derangement, whether overt or subclinical are increasing, being implicated as a major cause of clinical deterioration in cancer patients.

Both haemorrhagic and thromboembolic manifestations have been shown to occur in neoplastic diseases with the latter being more frequently seen in solid tumours while haemorrhage is one of the principal symptoms associated with leukaemias. Ambrus and associated in the year 1975 reported that thrombosis and/or bleeding was the second most common cause of death in hospitalised cancer patients.[3] Severe haemorrhage is however seen especially in widespread malignancies like in the lung, stomach, colon, breast and in malignant melanoma.[4]

Tumour cells activate the haemostatic system in various ways. They may release procoagulant tissue factor, cancer procoagulant (cysteine proteinase), inflammatory cytokines and micro-particles which directly causes activation of the coagulation cascade or they may activate the host's haemostatic cells by either direct release of soluble factors or by direct adhesive contact, thereby enhancing clotting activation.

**OBJECTIVES:**

- To evaluate different types of haemostatic abnormalities in haematological and epithelial malignancies, especially the head and neck epithelial malignancies.
- To look for the differences in the grades of these abnormalities in metastatic & non-metastatic malignant conditions.

**MATERIALS AND METHODS**: The study was conducted in the Department of Pathology, Gauhati Medical College & Hospital, Guwahati from July 2004 to June 2005. Total 70 cases having head and neck epithelial malignancies, oesophageal cancers, acute leukaemias, chronic leukaemias and lymphomas were selected from among the patients attending the different specialties of Gauhati Medical College and Hospital, Guwahati.

The battery of tests performed on each patient were: peripheral blood smear stained with Leishman stain for microangiopathic haemolytic anaemia, platelet count done both manually and automated; bleeding time by Ivy method; whole blood clotting time by Lee and White's method 1973; Prothrombin time, activated partial thromboplastin time and plasma fibrinogen values found out with the help of coagulometer using platelet poor plasma and XI (cross-linked)fibrin degradation product positivity in plasma by latex agglutination method.

A group of sixty healthy subjects of both sexes and matched age groups were selected as controls. Consent was taken from each patient and all the findings were noted in the proforma prepared for the study.

**RESULTS AND OBSERVATION:**

| Age group | Male | Female | Percentage |
|---|---|---|---|
| 0 – 10 years | 5 | 0 | 7.14% |
| 11 – 20 years | 3 | 2 | 7.14% |
| 21 – 30 years | 1 | 2 | 4.29% |
| 31 – 40 years | 5 | 2 | 10.00% |
| 41 – 50 years | 10 | 5 | 21.42% |
| 51 – 60 years | 18 | 6 | 34.29% |
| 61 – 70 years | 7 | 1 | 11.42% |
| 71 – 80 years | 2 | 3 | 4.29% |
| **Total Cases** | **51** | **19** | **100%** |

***Table 1: Showing the Age and Sex Distribution of the Cases***

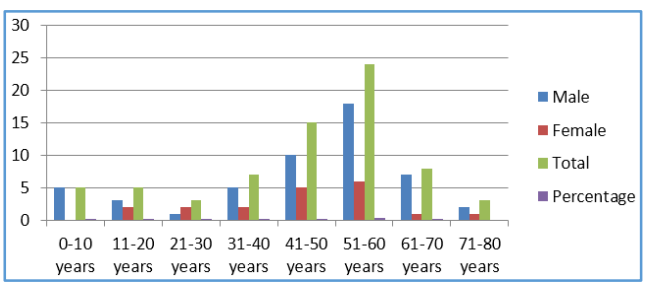


***Chart 1: Showing the Age and Sex Distribution of Cases***

| Type of cases | No of cases | Percentage |
|---|---|---|
| Metastatic | 22 | 28.57% |
| Non-metastatic | 29 | 44.29% |
| Systemic | 19 | 27.14% |
| | 70 | 100% |

***Table 2: Showing the Percentage of Case of Metastatic, Non-metastatic & Systemic (Leukaemias and Lymphomas) Malignancies***

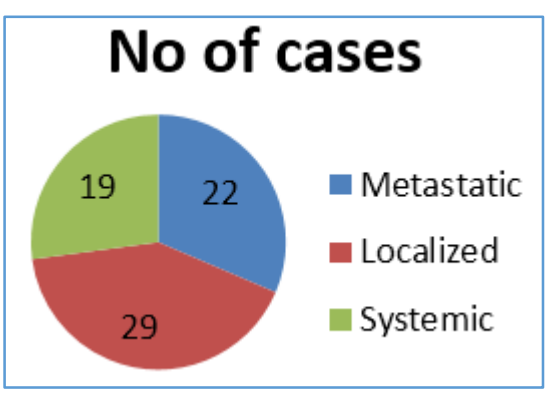


***Chart 2: Pie Diagram Showing the Percentage of Case of Metastatic, Non-metastatic & Systemic (Leukaemias and Lymphomas) Malignancies***

| < Normal range | Normal range | >Normal range |
|---|---|---|
| Platelet count-11 | 54 | 5 |
| Bleeding time-32 | 37 | 1 |
| Clotting time-5 | 63 | 2 |
| Prothrombin time-4 | 51 | 15 |
| APTT-5 | 50 | 15 |
| Fibrinogen-4 | 30 | 36 |

***Table 3: Showing Distribution of Cases Around Normal Range***

| No. of abnormal tests | No. of cases | Percentage of cases |
|---|---|---|
| 1 | 13 | 18.57% |
| 2 | 16 | 22.86% |
| 3 | 19 | 27.14% |
| 4 | 12 | 17.14% |
| 5 | 4 | 5.71% |
| 7 | 1 | 1.43% |
| **Total** | **65** | **92.85%** |

***Table 4: Showing Number of Abnormal Tests***

| Sl. No. | Result | No. of cases | Percentage of cases |
|---|---|---|---|
| 1 | Positive serum FDP | 41 | 58.57% |
| 2 | Hyperfibrinogenaemia | 36 | 51.43% |
| 3 | Shortened BT | 32 | 45.71% |
| 4 | Thrombocytopenia/ Thrombocytosis (11/5) | 16 | 22.85% |
| 5 | Prolonged PT | 15 | 21.48% |
| 6 | Prolonged APTT | 14 | 20.00% |
| 7 | Prolonged WBCT | 02 | 2.86% |

***Table 5: Showing Common Abnormalities in Order of Frequency***

FDP- Fibrin degradation products, BT- Bleeding time, PT-Prothrombin time, APTT- Activated partial thromboplastin time, WBCT- Whole blood clotting time

| Test | No. of abnormal results | Low values | High values |
|---|---|---|---|
| Platelet Count | 5 | 1(4.55%) | 4(18.18%) |
| Bleeding time | 11 | 11(50.00%) | 0 |
| Clotting time | 3 | 1(4.55%) | 2(9.09%) |
| Prothrombin time | 7 | 2(9.09%) | 5(22.73%) |
| APTT | 6 | 3(13.64%) | 3(13.64%) |
| Fibrinogen | 13 | 0 | 13(59.09%) |

***Table 6: Showing the Distribution of Abnormal Values in Metastatic Cases (22 cases)***

| Test | No. of abnormal results | Low values | High values |
|---|---|---|---|
| Platelet Count | 2 | 2(6.98%) | 0 |
| Bleeding time | 15 | 15(51.72%) | 0 |
| Clotting time | 2 | 2(6.98%) | 0 |
| Prothrombin time | 5 | 2(6.98%) | 3(10.35%) |
| APTT | 5 | 2(6.98%) | 3(10.35%) |
| Fibrinogen | 16 | 2(6.98%) | 14(48.28%) |

***Table 7: Showing the Distribution of Abnormal Values in Non-Metastatic Cases (29 cases)***

| Test | No. of abnormal results | Low values | High values |
|---|---|---|---|
| Platelet Count | 10 | 9(47.37%) | 1(5.26%) |
| Bleeding time | 7 | 6(31.58%) | 1(5.26%) |
| Clotting time | 2 | 2(10.53%) | 0 |
| Prothrombin time | 7 | 0 | 7(36.84%) |
| APTT | 9 | 0 | 9(47.37%) |
| Fibrinogen | 11 | 2(10.53%) | 9(47.37%) |

***Table 8: Showing the Distribution of Abnormal Values in Systemic Malignancy Cases (19 cases)***

| Case group | No. of FDP+ve cases | Total no of cases | Percentage |
|---|---|---|---|
| Metastatic | 19 | 22 | 86.36% |
| Localised | 10 | 29 | 24.39% |
| Systemic | 12 | 19 | 63.16% |

***Table 9: Showing the Number of Metastatic, Localised and Systemic Malignancies with FDP in Serum***

FDP- Fibrin degradation products.

**DISCUSSION**: In the study of seventy cases, we got 44 cases of head & neck epithelial malignancies, 7 cases of upper 1/3 oesophageal cancers, 12 cases of leukaemia & 7 cases of lymphomas of both sexes & different age groups prior to therapeutic intervention. The commonest age group affected was 51 – 60 yrs. and male: female was 3.7:1.

The number of metastatic cases were 22, non-metastatic cases were 29 & 19 cases belonged to leukaemias and lymphomas. We found 65 out of 70 malignant cases (92.85%) showed at least one abnormal test of coagulation. Bick R.L (1978) and others found that a hypercoagulable state is common in both leukaemias and solid tumours.[4] Increased pro-coagulant activities have been demonstrated in certain malignant condition like acute promyelocytic leukaemia often leading to DIC without symptoms.[5]

The most frequent abnormality in our study was 41 cases (58.57%) of FDP positivity in their serum followed by 36 cases (51.43%) of hyperfibrinogenaemia, 32 cases (45.71%) shortened bleeding time, 16 cases (22.85%) revealing thrombocytopenia/thrombocytosis, 15 cases (21.48%)revealing prolonged PT. There were 14 cases (20%) showing prolonged APTT (studies earlier found similar)[6,7,8] & 2 cases only showing prolonged clotting time. Activated coagulation in cancer leads to formation of increased fibrin deposition (hyperfibrinogenaemia) stimulated by tissue factor activity by the destroyed tissues;[6,9] positive fibrin degradation products i.e. indication of ongoing fibrinolytic process is found in serum due to the increased plasminogen activator expression;[7,8,10,11] shortened BT is probably due to increased platelet aggregation by the micro vesicles shed by tumour cells,[12,13] and also the thrombin generated by the tumour associated pro coagulant activity may also lead to increased platelet aggregation;[14] prolonged PT & APTT were due to reduced levels of many clotting factors say factor II, V, VII & X either singly or in combination.

Tissue factor can lead to the formation of both localised as well as systemic procoagulant states, their action being potentiated by phosphatidylserine and heparanase which help in the spread of the tumour. Moreover, tumour cells express plasminogen activators (u-PA and t-PA), their inhibitors (PAI-1 and PAI-2), receptors like u-PAR for their fibrinolytic activity. Many pro inflammatory molecules like growth factors and cytokines secreted by the tumour cells induce tissue factor production, PAI-1 production along with down regulation of thrombomodulin and upgradation of cell adhesion molecules.[15]

The tumour cells directly activate fibrinolysis or get activated by thrombin formation due to interactions between tumour cells and host tissue components.[16,17] Most cancer patients however maintain a delicate balance between the two system of coagulation and fibrinolysis.[8] Sun in the year 1979 showed the evidence of subclinical thrombotic and/or fibrinolytic activity in the form of abnormal tests in nearly 95% of cases.[7] Soong and Miller[18] found the mean fibrinogen level in cancer patients to be 191- 524 mg/dL as compared to normal levels of 200- 400 mg/dL, the highest levels in lung and breast. Carlson (1973) reported the findings of FDP in the sera of 41% patients with cancer, 85% in patients with remote metastases but 30% with regional lymph node metastases.[11]

But in our study, we also found decreased platelet count probably due to their consumption in the disseminated coagulative process & increased platelet count due to compensatory over production following a low grade intravascular coagulation and by the direct stimulus by the tumour cells.[8] Shortened whole blood clotting time (WBCT) may be due to increased levels of factor I, II, V, VIII, IX and XI. Prolonged WBCT was seen in 2 cases of metastatic cancers with FDP positivity and thrombocytosis. Shortened PT was due to extrinsic pathway activation by tissue factor. Shortened APTT may be due to raised levels of factor V, VIII & XI and due to tumour neo vascularisation activating the contact system. The dropping levels of fibrinogen may be the onset of a consumptive process.

| Test | Range | Mean | SD | P value |
|---|---|---|---|---|
| Platelet count | 25-450 x 10/L | 226.14 | 110.34 | >0.05 |
| Bleeding time | 0.45-10.0 mins. | 1.94 | 1.29 | <0.01 significant |
| Clotting time | 2.05-6.50 mins. | 3.93 | 0.94 | >0.05 |
| Prothrombin time | 9-24 secs | 14.65 | 3.68 | <0.01 significant |
| APTT | 19-84 secs | 37.21 | 10.10 | <0.01 significant |
| Fibrinogen | 116-600 mg/dL | 407.2 | 126.67 | <0.01 significant |

***Table 10: Showing the Range of Values in Various Tests in the Malignancy Cases***

| Test | Metastatic group Mean±SD (22 cases) | Non-metastatic group Mean±SD (29 cases) | P value |
|---|---|---|---|
| Platelet count | 275.45±124.95 | 214.14±63.33 | >0.01 |
| Bleeding time | 1.83±0.78 | 0.55±0.71 | <0.01 |
| Clotting time | 4.14±1.15 | 3.68±0.76 | <0.01 |
| Prothromb in time | 15.11±3.94 | 13.53±3.91 | <0.01 |
| APTT | 37.3±10.52 | 35.34±11.47 | >0.01 |
| Fibrinogen | 439.18±111.02 | 389.76±133.89 | <0.01 |

***Table 11: Comparing the Metastatic Cases with Non-Metastatic Cases (p value<0.01 in all Except PC & APTT)***

| Test | Systemic group Mean±SD (19 cases) | Non-metastatic group Mean±SD (29 cases) | P value |
|---|---|---|---|
| Platelet count | 187.37±149.07 | 214.14±63.33 | >0.01 |
| Bleeding time | 2.58±2.23 | 0.55±0.71 | <0.01 |
| Clotting time | 4.06±0.97 | 3.68±0.76 | >0.01 |
| Prothromb in time | 15.82±3.18 | 13.53±3.91 | >0.01 |
| APTT | 39.97±7.59 | 35.34±11.47 | >0.01 |
| Fibrinogen | 396.79±138.71 | 389.76±133.89 | >0.01 |

***Table 12: Comparing the Systemic Cases with Non-Metastatic Cases (p value >0.01 in all Except BT)***

We had taken up this study to look for the incidence and types of haemostatic abnormalities seen in cancers and also to look if there any difference between metastatic and localised or non-metastatic cancers and also between localised cancers and haematological malignancies. (leukaemias and lymphomas).

The patients were categorised according to the number of abnormal tests and it was found that majority of patients showed at least 3 abnormal findings and some more than three which was a significant finding. Metastatic group values were more than localised group, so statistically significant.

100% metastatic cases (22) showed one abnormality at least with 13 cases of hyperfibrinogenaemia, 12 cases of FDP positivity, 11 cases of shortened BT, 5 cases of prolonged PT, 4 cases of increased platelet count, 3 cases of APTT.

86.21% (25 out of 29) localised malignancy cases showed one or multiple abnormalities meaning 4 case showed no abnormality at all. However, the most important finding was high values of plasma fibrinogen in 14 cases. Bleeding time was low in 15 cases; PT and APTT were high in 3 cases and low in 2 cases; platelet count and clotting time were low in two cases.

18 out of 19 systemic malignancies showed one abnormal test. APTT and plasma fibrinogen was prolonged in 9 cases whereas 7 cases had prolonged PT. The single case with 7 abnormal tests was a case of acute lymphoblastic leukemia. Meddeb B, Guermazi et al (2001) researched studies which showed low fibrinogen level, elevated D-dimer, decreased factor V and normal anti-thrombin III value. They found enzymatic proteolysis of fibrinogen by the blast cells and this mechanism could count for the haemostatic abnormalities.[19] This was seen in our study in a case of ALL with low fibrinogen and positive FDP in serum. Studies show that haemostatic abnormalities and thrombotic disorders were more in malignant lymphoma with a significant rise in plasma fibrinogen and D-dimer level s than healthy subjects.[20]

There is a definite correlation between cancer and clotting mechanism which is supported by immunohistochemical and electron microscopical studies of histological specimens that demonstrate the presence of fibrin, the final product of coagulation cascade within and around primary and metastatic tumours along with platelet microthrombi in association with the tumour cells.[21]

Recent updates of molecular studies demonstrate in experimental models that oncogene and repressor gene mediated neoplastic transformation activate clotting which is thought to be an important step of neoplastic transformation.[22]

**CONCLUSION:** From the present study, we can conclude that haemostatic abnormalities, isolated to multiple are frequently associated with malignant diseases, even before the institution of any form of chemotherapy or radiotherapy or surgery. The range of the haemostatic disorders in general, were more pronounced in the metastatic group. So, it is important to monitor the haemostatic profile of a cancer patient during the course of the disease and treatment to detect the disturbed haemostatic-fibrinolytic balance which may lead to life threatening complications. The basic screening tests in our study done in a government hospital setup are affordable and sensitive to assess the prognostic value of routine tests of coagulation while predicting the outcome of the patient. But it is also true that they do not possess 100% clinical value to predict an impending phenomenon of thromboembolism and prognosis of the patient unless supplemented by coagulation assays and markers.

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