Original Article

Evaluation of Coagulation Abnormalities in Lung Cancer Patients

Ikram Din Ujjan, Nisar Ahmad Khokhar, Muzaffar A Shaikh, Imran Ali Shaikh, Rashid Ahmed Memon and Narinder Maheshwari

ABSTRACT

OBJECTIVE: To determine the coagulation abnormalities in patients with lung cancer.
STUDY DESIGN: Case-control study.
PLACE AND DURATION: Department of Pathology Isra University Hospital Hyderabad, Sindh – Pakistan, and Department of Medicine Liaquat University of Medical & Health Sciences Jamshoro, Sindh – Pakistan, from June 2006 to December 2007.
PATIENTS AND METHODS: Seventy subjects were recruited for the study by non-probability convenient sampling technique. Forty freshly diagnosed histopathology proven lung cancer patients were taken as cases, whereas 30 healthy subjects comprised the control group. Platelet count (PLT) was done on hematology analyzer while prothrombin time (PT), activated partial thromboplastin time (APTT) and plasma D-dimer tests were performed by commercially available kits at Department of Pathology, Isra University Hospital Hyderabad, Sindh – Pakistan. T-test was applied to determine the significance of differences between two groups whereas P-value up to .05 was taken as significant.
RESULTS: The mean±SD PLT in cases and controls was 394±170 and 216±73 respectively. The mean±SD values for these respective groups were for PT 14.7±0.5 and 12.6±0.4, for APTT 41.5±6.2 and 25.8±3.7. D-dimer levels were <500 in all 30 controls whereas these were up to 2000 in cases.
CONCLUSION: There is a strong relationship between coagulation abnormalities and lung cancer. D-dimer is very sensitive for evaluation of fibrinolyis related with lung cancer.

KEYWORDS: Coagulation abnormalities, lung cancer, D-dimer, platelet count, prothrombin time, activated partial thromboplastin time.

INTRODUCTION

Lung cancer is the leading cause of cancer death for both men and women. About 85% of patients who develop lung cancer die from it.[1] Coagulation of fibrinolytic system activation is present in lung cancer patients at clinical or subclinical levels.[2] The biological significance of the hemostatic abnormalities in cancer is not clear. There is some evidence to suggest that the capacity of neoplastic cells to activate the coagulation system and to express increased fibrinolytic activity facilitates their growth and contributes to their invasive and metastatic behavior.[3] There is a complex interaction, which has an important role in the course of the disease, between pathogenetic mechanism of thrombosis, tumor cells, hemostatic systems, and patient characteristics.[4] The interaction between malignancy and coagulation/fibrinolysis is the pathogenesis of disseminated intravascular coagulation (DIC) that occurs in malignancy.[5] Determination of coagulation and fibrinolytic system markers may be important in the evaluation of their relationship with disease stage, performance status of the patients, and survival as well as in the selection of treatment that will be administered to the patient.[2] It has been reported that number of coagulation factors are important independent predictors of survival, e.g. prothrombin time (PT), platelet count (PLT), activated partial thromboplastin time (APTT), fibrinogen and D-dimer.[6] D-dimers are formed by the degradation of cross-linked fibrin in all conditions where coagulation and fibrinolytic systems are activated. It is increased in certain medical conditions including pulmonary embolism, solid tumors, DIC, pregnancy, preeclampsia, etc.[7] Plasma concentrationof D-dimer is increased either due to increased production or decreased excretion.[8] In contrast to other markers of homeostasis, D-dimer is a relatively more convenient and more stable marker to measure, which can be performed by inexpensive and simple methods.[2]

The purpose of this study is to evaluate the coagulation abnormalities in patients of lung cancer, which may help and inspire our clinicians to conduct larger studies to evaluate this important aspect.

PATIENTS AND METHODS

This case-control study was conducted to determine the coagulation abnormalities in patients with lung cancer, at Department of Pathology Isra University

Hospital Hyderabad, Sindh Pakistan and Department of Medicine Liaquat University of Medical and Health Sciences Jamshoro, Sindh – Pakistan, from June 2006 to December 2007. Well informed consent was obtained from all subjects. Forty cases of freshly diagnosed, histopathology proven patients of lung cancer were labeled as Cases (study group) while 30 healthy volunteers were labeled as Controls (control group), all were selected by non-probability convenient sampling method. Patients with malignancies other than lung cancer, with pre-existing coagulation disturbances of other causes, on anti-coagulant therapy, with family history of coagulopathy were excluded from the study. There was no statistically significant difference of age, sex and sociodemography between the two groups.

Tumor staging was performed according to the standard procedures of new international staging system.

Blood samples were obtained (pretreatment in study group) using 10-ml disposable syringes. With aseptic measures 5-ml of blood was drawn from which 1.8 ml was mixed with 0.2 ml of sodium citrate for PT, APTT and D-dimer levels, while 2-ml of blood was transferred to EDTA collection tube for platelet estimation. Blood samples were processes immediately or, if needed, stored at -40°C. Commercially available reagents were used to measure PT (STA Neoplastin Plus kit), APTT (STA APTL LT kit) and D-dimer (STA LIATEST D-DI kit).

A predesigned proforma was used to record data regarding sociodemographic profile, physical examination, biochemical laboratory test results, imaging studies, bronchoscopy findings, histopathological evaluation results of biopsy and sputum analysis. The references ranges were for PLT count 150-450 $x10^3$/µL, for PT 12-14 sec, for APTT 20-30 sec, and for plasma D-dimer level 0-500 ng/dL.

The means±SD were calculated for PT, APTT, PLT and D-dimer in both groups. T-test was applied to determine the significance of difference between both groups. P-values up to 0.05 were taken as significant. Data were analyzed by using SPSS version 13.0 for windows.

RESULTS

There was statistically significant difference in the mean±SEM of PT between two groups. The difference in APTT levels and PLT counts between both groups was highly significant **(Table I)**. D-dimer levels were found to be highly raised in cases than in controls **(Table II)**.

TABLE I:
COMPARISON OF HEMATOLOGICAL INVESTIGATIONS BETWEEN BOTH GROUPS (n=30)

	Cases	Controls	P-value
PT (sec)	14.7±0.5	12.6±0.4	0.0261
APTT (sec)	41.5±6.2	25.8±3.7	0.0027
PLT ($x10^3$/µL)	394±170	216±73	<0.001

TABLE II:
COMPARISON OF D-DIMER LEVELS BETWEEN BOTH GROUPS (n=30)

D-dimer level (ng/dL)	Cases	Controls
<500	17 (42.5%)	30
500 – 1000	14 (35%)	0
1000 – 2000	09 (22.5%)	0

DISCUSSION

Coagulation and fibrinolytic system constitutes an important component of the prognosis of lung cancer. This system plays significant role in various processes from the early period of tumor formation until the patient's death.[2] Approximately 90% of cancer patients with metastatic disease and 50% of all cancer patients have one or more abnormal coagulation parameters.[6] Several laboratory abnormalities have been described, including prolonged and shortened prothrombin time (PT), activated partial thromboplastin time (APTT), increased and decreased levels of Factor II, Factor V, Factor VIII, Factor IX, Factor XI, Factor XII, fibrinogen (F), F/fibrin degradation products, the thrombin-antithrombin III complex (TAT) and thrombocytosis.[6,9]

In present study PT, APTT, PLT and D-dimer levels in freshly diagnosed lung cancer cases were compared with healthy controls. It was observed that PLT were increased in study group than in control group and the difference was highly significant (P<0.001). Similar results have been observed by Karagoz and colleagues in their study who also reported significantly increased PLT in lung cancer patients than in healthy controls (P=0.011).[10] Altiay and associates also reported increased PLT in lung cancer patients.[11]

In this study the cases of lung cancer had significantly prolonged PT than controls (P=0.026). In contrast Ferrigno D and associates reported decreased PT in 4% of their cases and none of their subjects had prolonged PT.[6] However they recruited the patients who were at early stages of their disease, which may be the reason of this difference of observations.

We found that APTT was comparatively prolonged in

study group than control group, as also reported by Seitz and coworkers.[12]

D-dimer is the smallest degradation product of fibrin, resulting from the proteolytic action of plasmin.[13] Plasma D-dimer levels were found to be highly raised in study group and the difference was highly significant (P<0.001). Many studies have reported their results that are in support of this study and had observed very high plasma D-dimer levels in patients with lung cancer, particularly in those who had extensive disease.[2,14-16]

CONCLUSION

It was observed in this study that coagulation and fibrinolytic abnormalities are strongly associated with lung cancer and plasma D-dimer levels are found very high in these patients, hence can be used as a predictive factor in cases of lung cancer. Further large studies are needed to be conducted in our setup to evaluate the effective prognostic value of coagulation abnormalities in detail so that the therapeutic interventions aimed to correct the activation of the coagulation-fibrinolytic system may be considered.

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AUTHOR AFFILIATION:

Dr, Ikram Din Ujjan *(Corresponding Author)*
Assistant Professor, Department of Pathology
Isra University Hospital Hyderabad, Sindh-Pakistan.
E-mail. ikramujjan1973@yahoo.com

Dr. Nisar Ahmad khokhar
Registrar, Department of Medicine,
Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, Sindh-Pakistan.

Dr. Muzaffar A. Shaikh
Assistant Professor, Department of Medicine
LUMHS, Jamshoro, Sindh-Pakistan.

Dr. Imran Ali Shaikh
Assistant Professor, Department of Medicine
Isra University Hospital Hyderabad, Sindh-Pakistan.

Dr. Rashid Ahmed Memon
Professor, Department of Pathology
Isra University Hospital Hyderabad, Sindh-Pakistan.

Dr. Narinder Maheshwari
Trainee Registrar, Department of Medicine
Liaquat University Hospital Hyderabad, Sindh-Pakistan.