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ORIGINAL ARTICLE

Association between Disease Severity and Coagulation Profile in Lung Cancer Patients

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ABSTRACT

The main idea behind this study is to assess the extent of derangement of coagulation parameters, prothrombin time (PT) and activated partial thromboplastin time (APTT), in lung cancer as occurrence of these abnormalities may be associated with excessive bleeding.

Objectives: To find out the association between disease severity and coagulation profile in lung cancer patients.

Materials & Methods: Sixty patients with lung cancer were included in the study from pulmonology department, Allama Iqbal Memorial Teaching Hospital, Sialkot. Two groups were formed from the chosen patients. 15 healthy, age- and sex-matched controls were included in group A, while 45 patients with a histological diagnosis of lung cancer were included in group B. There was no history of coagulation disorders or anti-coagulant therapy in selected patients. PT, APTT, Fibrinogen, FDP's were recorded.

Result: The median age was 49 years (range from 13 to 62 years) with male to female ratio of 1.8:1.Among them, 70% of lung cancer patients had history of smoking and 17.77% had stage Ib, 22.22% had IIb, 8.88 % IIIa, 33.33 IIIb, 17.77 % had stage IV disease. Histologic sub-type were Non-small cell lung cancer (NSCLC) 40 %, Small cell lung cancer (SCLC) were 13.3 %, Squamous cell cancer were 33.33 %, adenocarcinoma 11.1 % and large cells cancer were 2.2 %. The Mean ± SD value for these respective groups were PT (Sec) 15.16±3.8 and 12.4±0.1, for APTT (Sec) 37.7±4.9 and 25.26±1, for Fibrinogen (mg/dl) 299.5±33.6 and 285.3±43.65 respectively. Quantitative estimation of FDPs were done in all. Elevated levels of FDP (≥ 10 µgm/mL) were found in 23 patients.

Conclusions: High coagulation parameter levels were linked to advance cancer staging, according to this study, and these parameters may be utilised to forecast how severe a patient's lung cancer will be.

Keywords: Disease Severity, Lung Cancer, coagulation disorders

INTRODUCTION

Lung cancer is one of the most prevalent malignancies in the world[1-2]. Lung cancer is currently the most common malignant disease and the leading cause of cancer related-deaths in all age groups and in both sexes[3]. Lung cancer is the most frequent occurring cancer and leading cause of cancer death worldwide[4]. Patients with malignant tumors often have systemic blood coagulation dysfunction, the relationship between cancer and coagulation is characterized by several mechanism pointing that tumour biology and coagulation are closely linked process[5].

The association between cancer and hemostatic system has been known since Trousseau's study from the 19th century[6]. Coagulation or fibrinolytic system activation is present in lung cancer patients at clinical or subclinical level. There is a complex interaction, which has an important role in the course of the disease, between pathogenetic mechanisms of thrombosis, tumor cells, homeostatic systems, and patient characteristics. Patients with deep venous thrombosis (DVT) or subclinical hypercoagulopathy usually have worse prognosis. Activation of the coagulation system not only plays a role in the local and systemic dissemination of the disease, but also has a significant impact on mortality and survival rate by leading to thromboembolic events[7]. The coagulation system is activated through thrombin formation and fibrinolytic system through plasminogen activators[8-9]. Hypercoagulability disorders are associated with a variety of malignancies including lung cancer[10]. A hypercoagulable state is observed in lung cancer patients which is expressed as thrombosis, haemorrhage or low grade DIC [11]. The tumor can induce a pro-coagulant state, and the activated coagulation factors then promote tumor growth, infiltration, metastasis, and angiogenesis[12,13].

The most prevalent plasma coagulation factor, fibrinogen, is produced by hepatocytes. The formation of platelet-fibrin tumor cell aggregates may cause adhesion to endothelial cells and confers metastasis potential[14].

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Coagulation disorders are a common problem in neoplastic patients and many factors increase the risk of thromboembolic events in these patients[15].The complications of neoplastic disease are hemorrhages and DIC syndrome because neoplastic cells react directly with the system of coagulation and fibrinolysis producing procoagulants and plasminogen activators[16]. Tumor cells release proteases into interstitial fluid at a higher rate than normal cells, which contributes directly to the invasiveness of tumor cells and to the destruction of the adjacent host tissue[17]. These proteases act on proteins and coagulation cascade leading to the formation of fibrin which is found at the invanding periphery of malignant neoplasms. Malignant cells induce local fibrinolysis due to high levels of plasminogen activator. The coagulation and fibrinolytic abnormalities are often present in lung cancer. A prolonged value of prothrombin time and higher values of platelet count, fibrinogen and D-dimer are all associated with a poor prognosis in lung cancer patients. A prethrombotic state is probability involved in the mechanism of metastatic spread which is depicated by a prolongation of prothrombin time is confirmed as an aggravating condition in lung cancer[18-19]. Activation of coagulation and fibrinolysis with-in tumour tissues is thought to be associated with tumour growth and metastasis in lung cancer[20]. The interactions between malignancy and coagulation or fibrinolysis are the pathogenesis of DIC that occurs in malignancy [21]. Slightly increased in patients with low and high fibrinogen levels showed the activation of fibrinolysis in patients of DIC[22]. High levels of circulating biomarkers resembling activated coagulation and fibrinolytic system such as fibrinogen, fibrinogen split products and D-dimer have been associated with decreased survival for several tumour types in previous studies[23-24]. This study aimed to investigate the incidence of some coagulation parameters abnormalities in lung cancer patients and attempted to evaluate the correlation of these coagulation tests with other clinic-pathologic variables.

MATERIAL AND METHODS

Total 60 patients were included in the present study. 45 patients histologically diagnosed cases of lung cancer from oncology

department, Ghulab Devi Hospital and Mayo Hospital lahore, who were admitted between Aug'2017 to Nov'2018. The control group consisted of 15 healthy individual without comorbidity. Lung cancer staging was performend for all patients according to the 7th TNM classification. The inclusion criteria were as following histologically diagnosed cases of lung cancer pretreatment were sellected. Patients with a history of venous thrombosis or anticoagulation therapy, hypertension, cardiovascular and cerebrovascular disease, diabetes, acute or chronic inflammatory disease, or previous malignancy were excluded from the current study.

Written informed consent was obtained from the patients before the sample collection. Blood samples were collected in the disposable syringe and put in to vacutainer tubes containing anticoagulant ciratate buffer 1:9, buffer for PT, APTT, FDPs and fibrinogen assay. History and clinical features were recorded in all subject in peroform. The blood sample were investigations for coagulation profile. The principales of differents tests and their procedures are adopted accordingly. They were centrifuged and the plasma was separated. PT,APTT, Fibrinogen, assay and quantitative estimation of FDPs were recorded.

RESULTS & OBSERVATIONS

Comparison of coagulation tests between patients and healthy controls: The plasma level of all coagulation tests including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (F), and Fibrin Degradation Products (FDPs). Revealed statistically significant difference between patient and control group (p <0.001 for all variables but for PT; p 0.045).

A summary of results of PT, APTT, fibrinogen, FDPs level and Characteristics of the patients is shown in Table 1,2,3,4,5,6 respectively.

Table 1: PT in patients of lung cancer and Control group

PT (Sec)	Group (A) (Control)	Group(B) (Patients with Lung Cancer)
Mean±SD	12.4±0.1	13.98±2.46
Range	11 – 14	13 – 21
Total patients	15	45

Statistical Analysis A Vs B: p<0.05 (S)

Table 2: APTT in patients of lung cancer and Control group

APTT (Sec)	Group (A) (Control)	Group(B) (Patients with Lung Cancer)
Mean±SD	25.26±1	37.7±4.9
Range	23 – 27	30 – 55
Total patients	15	45

Statistical Analysis A Vs B: p<0.05 (HS)

Table 3: PT, APTT, Fibrinogen and FDPs levels in cancer patients

Test	Normal range	Low		Normal		High	
		No	%	No	%	No	%
Prothrombin Time(PT)	11 – 15 Sec	-	-	30	66.66	15	33.33
Activated prothromboplastin time(APTT)	30 – 40 Sec	-	-	35	77.77	10	22.22
Fibrinogen assay	200-400 mg/dL	7	15.55	30	66.66	8	17.77
FDP level	10 µgm/mL	–	–	22	48.88	23	51.11

Table 4: FDPs in patients of lung cancer and Control group

FDPs (µg/ml)	Group (A) (Control)	Group(B) (Patients with lung cancer)
10	15 (100)%	22 (48.88%)
40	-	15 (33.33%)
80	-	8 (17.77%)
Total patients	15(100)%	45 (100%)

Statistical Analysis A Vs B: p<0.01 (HS)

Table 5: Characteristics of the patients (n=30)

Characteristic	Median (quartile) or frequency
Gender (male/female)	18/12
Age (years)	39.433± 5.11
Sokinmg (yes/no)	22/08
Histological type	
Non-small cell lung carcinoma	09
small cell lung carcinoma	03
Squamous cells carcinoma	10
Asenocarcinoma	05
Large cell carcinoma Stage	03
Stage Ib	04
IIb	06
IIa	02
IIIb	11
iv	07
Fibrinogrn(mg/dl)	Mean±SD 299.5±33.6 (210-400)
Prothrombin Time (PT)	Mean±SD 13.98±2.46
Activated prothromboplastin time (APTT)	Mean±SD 37.7±4.9

Table 6: FDPs levels according to stages in lung cancer (µg/dl)

FDPs		
Stages	FDPs (µg/ml)	No. of Patients
IB	10 (µg/ml)	09
IIB	10 (µg/ml)	06
IIIA	10 (µg/ml)	07
IIIB	40 (µg/ml)	15
IV	80 (µg/ml)	08

DISCUSSION

The blood coagulation scheme has been divided into two pathways, "extrinsic" and "intrinsic" both of which coproduction of thrombin. Approximately 80% of all cancer patients have abnormal coagulation parameters. Coagulation activation is common in cancer patients and is associated with a poor prognosis.[25,26] Activation of the hemostatic system is involved in tumor development, dissemination, and metastasis,[27,28] and activation of fibrinolysis secondary to coagulation activation is a well-recognized complication in patients with lung cancer[29]. The D-Dimer and FDP tests are very useful for the rapid diagnosis of DIC[30]. The prothrombin time (PT) and activated partial thromboplastin time (APTT) may be prolonged or shortened; hyperfibrinogenemia is common but acquired dysfibrinogenemia is rare unless the liver is involved. Intravascular activation of coagulation and fibrinolysis occur together cancer patients may have shortened euglobulin clot lysis times, decreased plasminogen levels, and an increase in plasmin-antiplasmin complexes. Most patients with cancer complicated by acute DIC have elevated FDP levels. The likelihood of increased FDP is greater in patients with remote metastases, compared to localized disease and may have prognostic value[30].

A systematic activation of clotting system has been observed in cancer patients which is usually reflected by subclinical abnormalities of conventional coagulation tests[31].

There is some evidence that the activation of coagulation and fibrinolytic system by neoplastic cells facilitates invasiveness and metastases[32]. Thus, the extent of such activation has been associated with tumor stage and prognosis in some malignancies such as breast, colorectal and lung cancer[33,34].

In the present study, FDP was found to be increased in 29 (45.5%) patients. It is believed that this moderate increase in FDP is a result of slow primary or a very low grade secondary fibrinolysis [35,36,37]. The present study indicates that elevated levels of FDP are common in cancer patients. This is as result of intravascular coagulation and secondary fibrinolysis which is not clearly defined, but it may be a slow and continuous introduction of

either a thromboplastin-like material or a plasminogen activator in circulation leading to consumption coagulopathy.

In the present study, FDPs were found to be significantly increased($p<0.01$) in patients of lung cancer when compared with control group. The increase level of FDPs were more in SCLC as compared to NSCLC. The FDPs levels were more increased in matastic disease as compared to localized disease. This increase was more in patients having DIC. There increased levels of FDPs may be due to enhanced fibrinolysis[38] observed elevated of FDPs in patients having malignancy.

The present study thus provides more reference values for patients with later-stage tumors and poorer overall condition. SCLC is a highly invasive tumor with a poor prognosis,[39] with different biological characteristics from NSCLC[41]. Valid biomarkers are therefore needed to determine the prognosis of SCLC. In the present study, pretreatment plasma D-dimer levels were independently in patients with SCLC. This conclusion is supported by previous studies of lung cancer in general [40,42,41,43].

CONCLUSIONS

In the present study, extensive (advanced) stages of disease were strongly associated with each of the coagulation parameters (PT, APTT, Fibrinogen level, FDPs respectively, although the histological types of lung cancer were not correlated with them. Further large studies on specific subgroups of lung cancer are needed to better define the effective prognostic values of the clotting abnormalities.

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