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Prognostic significance of hemostatic parameters in patients with lung cancer

Ebru Ünsal*, Figen Atalay, Sükran Atikcan, Aydin Yilmaz

Atatrk Chest Diseases and Thoracic Surgery Center, Ankara, Turkey

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Summary There is a subclinical activation of coagulation and fibrinolysis system in lung cancer. Alterations in hemostatic system are seen frequently in lung cancer correlated with the prognosis of disease. In this prospective study, our purpose was to investigate the prognostic significance of hemostatic markers in patients with lung cancer. The study comprised 58 patients (22 squamous cell carcinoma, 16 adenocarcinoma, 20 small cell carcinoma). There were 55 men (95%)and 3 women (5%) with a mean age of 61 years range (36–74). Plasma level of platelets (PLT), prothrombin time (PT), active partial thromboplastin time (aPTT), antithrombin III (AT III), fibrinogen (F) and D-dimer level were measured before the initiation of any therapy. Patients were followed up for 17 (12–20) months. The median survival was determined as 6.4 months. Three histopathologic groups; squamous cell carcinoma, adenocarcinoma and small cell carcinoma were compared for the hemostatic parameters. There were no statistically significant differences among the histopathologic types for any of the parameters ($P>0.05$). Patients were divided into two groups as patients without distant metastasis (stages I,II,III) and with distant metastasis (stage IV). The group with distant metastasis had higher level of D-dimer than the other group ($P<0.05$). However, there were no statistically significant differences for D-dimer level between stages IIIB and IV ($P>0.05$). Patients having high D-dimer and low AT III level had poor survival in our study. Thus, high level of D-dimer and low AT III level were determined as correlated with short survival ($P<0.05$). These results suggest that elevated plasma level of D-dimer and low AT III level might be a sign of poor prognosis in patients with lung cancer.

Introduction

There is a subclinical activation of coagulation and fibrinolysis system in cancer patients.[1] Hemostatic alterations are seen frequently in patients with lung cancer and the degree of coagulation and fibrinolysis activation has been found correlated with the clinical progression of the disease.[2] Tumor cells release either coagulation factors directly leading to coagulation pathway and thrombin formation or plasminogen activators directly activating the fibrinolytic system.[3,4] Thrombin leads to fibrin formation which acts as a growth factor for tumor cells and facilitates tumor angiogenesis. Fibrin deposition in cancer tissues serves as a barrier against the inflammatory cells that might destroy the tumor. Also, plasminogen activators generate plasmin which is an active serine protease of fibrinolysis. Plasmin promotes both tumor invasion and detachment of tumor cells into the circulating channels.[5,6]

*Corresponding author. Övecler 1. Cd. 48. Sk, No: 4/17, Dikmen, Ankara 06450, Turkey. Tel.: +90-312-478-3851; fax: +90-312-221-3276.
E-mail address: unsalebru@hotmail.com (E. Ünsal).

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In this prospective study, our purpose was to determine whether the hemostatic parameters are related to the histopathogical types, pretherapeutic tumor stages and prognosis in lung cancer.

Patients and methods

Patients

This prospective study included 58 patients with lung cancer. Diagnosis was performed by biopsies or cytological specimens taken at bronchoscopy, transthoracic needle aspiration or from surgical specimens. The types of tumors were grouped according to the World Health Organization Classification.[7] Patients having coagulation disturbances of other causes or taking oral anticoagulant therapy or with malignancies other than lung cancer were not included into the study.

In our study, 22 patients were diagnosed squamous cell carcinoma, 16 patients adenocarcinoma and 20 patients were diagnosed as small cell carcinoma. The group consisted of 55 men (95%) and three women (5%) with a mean age of 61 years range (36–74). Conventional radiographs, computerized tomography scanning, ultrasonography, gallium scintigraphy and bronchoscopic examination were performed for tumor staging based on the new international staging system.[8] There were three patients with stage IB, one patient with stage IIA, four patients with stage IIB, six patients with stage IIIA, 18 patients with stage IIIB and 26 patients with stage IV. Follow-up programs consisted of clinical, laboratory and radiological reassessments performed at 3–4 week intervals. Most of the patients received either chemotherapy (including platin regimens) or radiotherapy treatment. Only five patients received semptomatic therapy. The status of the patients who abandoned the follow-up program was informed by telephone interview with the patient or the family.

Methods

Before the treatment plasma was removed after the centrifugation of venous blood samples and five parameters; platelets (PLT), prothrombin (PT), active partial thromboplastin time (aPTT), D-dimer and fibrinogen (F) were all measured immediately except for antithrombin III (AT III). Blood samples were stored at $-20^{\circ}C$ until AT III analysis. Platelet counts were analyzed by automated complete blood cell counting devices on ethylenediamine tetra-acetic (EDTA) anticoagulated blood. Other parameters were measured by the BCS System, a high-speed random access analyzer (Dade Behring). PT, aPTT, F, D-dimer, AT III were all measured using commercially available reagent provided by Dade Behring. Thrombosel-S was used for PT measurement, prothrombin SL was used for the measurement of aPTT. Fibrinogen was determined by the Clauss method and Multitren U was used as a reagent. Plasma level of D-dimer was measured by using a latex enhanced turbidimetric test. AT III analysis was performed by using a chromogenic substrate and AT III concentration was assayed by the measurement of the color.

Statistical analysis

All statistical analyses were performed using the SPSS for windows release 9.0 package program. The results of PLT, PT, aPTT, D-dimer and AT III were reported as mean values $\pm$ standard deviation (SD). The correlation between the parameters and three histologic groups was evaluated by Kruskal–Wallis one-way analysis. The differences between patients without distant metastasis (stages I–II–III) and patients with distant metastasis (stage IV) for the variables were evaluated by Student's *t*-test. Multivariate survival analysis was performed using the Cox's regression model and survival curves were computed according to the method of Kaplan–Meier. A value of $P<0.05$ was accepted as statistically significant.

Results

Patients were followed up for 17 (12–20) months. The median survival was determined as 6.4 months. The reference value of each parameter is given in Table 1.

Comparison by histopathological types and tumor stages

Three histologic groups; squamous cell carcinoma, adenocarcinoma and small cell carcinoma were compared for the hemostatic parameters. There were no statistically significant differences among the histopathologic types for any of the parameters ($P>0.05$). The correlation between the histological types and hemostatic parameters is shown in Table 1.

Patients were grouped into two categories as having distant metastasis (stage IV) and patients without distant metastasis (stages I–II–III). Only plasma D-dimer level was significantly higher in

Table 1 Reference values of the variables and the correlation between the parameters and histopathological groups.

Parameters	Reference values	Squamous cell carcinoma	Adenocarcinoma	Small cell carcinom	*P*-value
PLT	150–400 $\times 10^3$/mm^3	410 ± 140.6	355.7 ± 136.26	339.55 ± 114.84	0.179
PT	10–15 s	12.41 ± 1.21	12.14 ± 1.56	12.63 ± 3.38	0.714
aPTT	25–45 s	33.35 ± 4.65	31.32 ± 3.52	31.8 ± 6.68	0.732
F	1.8–3.5 g/l	5.82 ± 2.12	5.72 ± 1.90	5.94 ± 2.02	0.788
D-dimer	125–375 μg/l	320.41 ± 171.72	340.65 ± 157.71	320.49 ± 202.59	0.867
AT III	75–125%	99.32 ± 21.42	102.14 ± 20.82	106.66 ± 16.93	0.314

Table 2 Comparison between patients without distant metastasis (stages I–II–III) and patients having distant metastasis (stage IV) for the hemostatic parameters.

Parameters	Stages I–II–III	Stage IV	*P*
PLT	390.71 ± 150.35	350.8 ± 116.39	0.272
PT	11.95 ± 1.3	12.93 ± 2.98	0.101
aPTT	31.54 ± 4.48	33.12 ± 5.86	0.251
F	5.8 ± 2.15	5.87 ± 1.88	0.893
D-dimer	285.6 ± 180.59	375.86 ± 160.48	0.04*
AT III	105.33 ± 18.16	98.65 ± 20.3	0.192

*$P < 0.05$ is statistically significant.

patients with distant metastasis than the other group ($P < 0.05$). Other parameters did not show any significant differences among the tumor stage (Table 2). Also, we compared stages IIIB and IV patients which are defined as extensive disease. There were no significant differences for the parameters between stages IIIB and IV ($P > 0.05$). However, stages I, II and III were not compared since the number of the patients was not enough for the statistical analysis.

Comparison by the survival of patients

Multivariate survival analysis was performed using the Cox's regression model. Other prognostic factors as age, sex, stage, histologic type, weight loss and ECOG performance status were all determined (Table 3). High plasma level of D-dimer showed a significant correlation with the short survival as median survival = 9.61 months for D-dimer < 375 μg/l versus median survival = 2.90 months for D-dimer > 375 μg/l (95% confidence interval (CI) 8.06–11.16 and 95% CI 2.20–3.61, respectively, $P = 0.000$). Also low level of AT III was significantly correlated with the short survival as median survival 4.07 months for AT III < 75% versus median survival 7.98 months for AT III ⩾ 75% (95% CI 1.75–6.40 and 95% CI 6.54–9.43 respectively, $P = 0.03$) (Figs. 1 and 2). Other parameters included PLT, PT, aPTT, F all were not determined as predictors of survival ($P > 0.05$). Only elevated D-dimer level and low AT III level were determined as a sign of poor prognosis in lung cancer (Table 4).

Discussion

Numerous studies have demonstrated the tendency of coagulation and fibrinolysis disorders to develop in cancer patients.[9,10] Basic hemostatic markers including PLT, PT, aPTT, F, D-dimer, AT III are found elevated in patients with lung cancer.[11,12]

In NSCLC and SCLC the mechanisms activating coagulation and fibrinolysis systems are different.[6] In SCLC tumor cells release tissue factor directly activating the coagulation system. However in NSCLC the host macrophages release procoagulant factors which activate the fibrinolysis system.[6,13] There are some studies having different results about the correlation between the histopathological types and hemostatic parameters.[2,10] In our study, we did not find statistically significant differences for any parameters between three histopathological types. Although Hagedorn et al. reported more extensive degree of clotting abnormalities in patients with adenocarcinoma and

squamous cell carcinoma, Seitz et al. found no significant differences between NSCLC and SCLC patients for the hemostatic markers.[2,14]

In most of studies[2,10] although hemostatic parameters do not show correlation with the histopathological types it is reported that there is a significant correlation between the parameters and tumor stage.[2] Clinical and experimental evidence supports the idea that activation of coagulation and fibrinolysis system plays an important role in tumor spreading.[4,15] In our study, we found only D-dimer level significantly elevated in patients with distant metastasis independently from the histological type. Also there are some studies supporting our result in which high D-dimer level was found in patients having distant metastasis.[2,10] However, in our study, we did not find any significant differences between stages IIIB and IV for D-dimer level. So, we conclude that D-dimer level is found elevated in extensive disease with local or distant metastasis.

In most of the studies it is reported that lung cancer patients having high D-dimer level have poor prognosis.[11,16,17] Taguchi et al. found D-dimer to be an independent predictor of survival in patients with lung cancer.[16] Similar to the previous studies,[16,17] we also performed multivariate survival analysis to determine the prognostic significance of hemostatic parameters and we found D-dimer level higher in patients having short survival. Pedersen et al. reported thrombocytosis as correlated with the poor survival[18]. Thrombocytosis was

Table 3 Characteristics of the patients in the study.

Histologic groups		
Squamous cell carcinoma	22	38%
Adenocarcinoma	16	28%
Small cell carcinoma	20	34%
TNM Stage		
Stage IB	3	5%
Stage IIA	1	2%
Stage IIB	4	7%
Stage IIIA	6	10%
Stage IIIB	18	31%
Stage IV	26	45%
Male	55	95%
Female	3	5%
ECOG PS 0–2	37	64%
3–4	21	36%
Age <70	8	14%
>70	50	86%
Weight loss $>10\%$	31	53%
$<10\%$	27	47%

Table 4 Multivariate survival analysis with high levels of PLT, PT, aPTT, F and D-dimer and low AT III level.

Parameters	Relative risk estimates	*P*-value
PLT $>400\times10^3/mm^3$	0.961	0.893
PT >15 s	1.463	0.529
aPTT >45 s	0.659	0.681
F >3.5 g/l	1.276	0.392
D-dimer >375 μg/l	10.946	0.000*
AT III $<75\%$	2.709	0.039*

*$P<0.05$ is statistically significant.

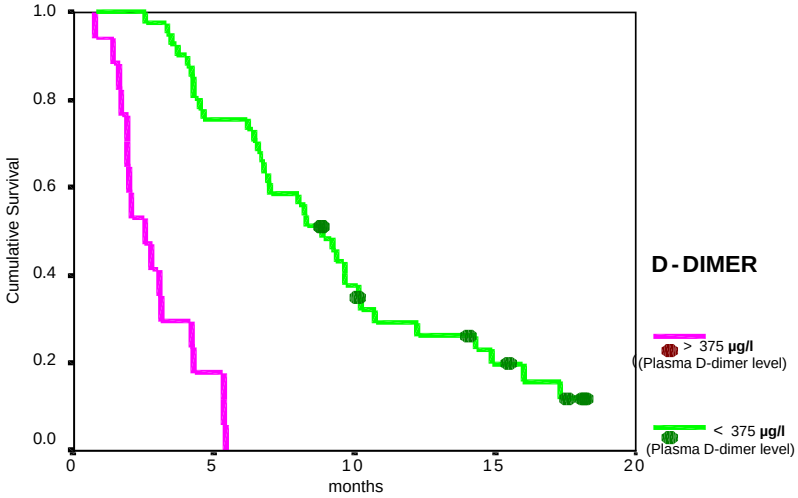

Figure. 1 Survival analysis of patients with lung cancer based on plasma level of D-dimer.

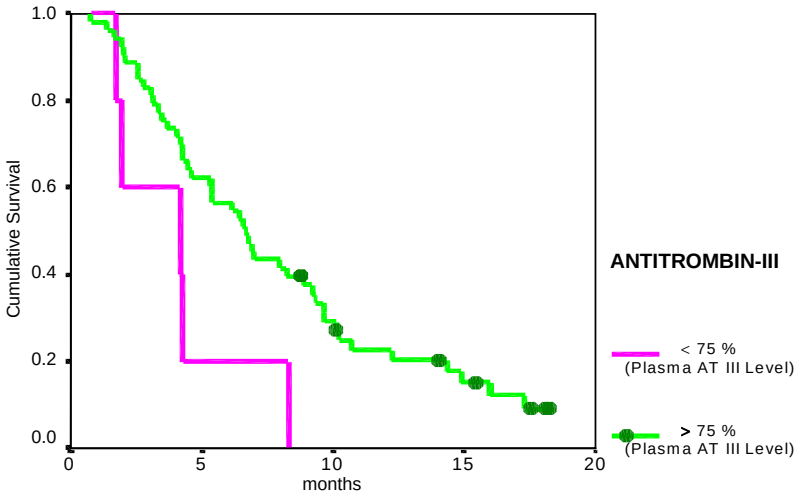

Figure. 2 Survival analysis of patients with lung cancer based on plasma level of AT III.

reported as being associated with the tumor load. In our study, thrombocytosis was not found as predicting prognosis. Also other parameters including PT, aPTT and F all did not show statistically significant correlation with the survival.

In lung cancer, the synthesis of anticoagulant proteins decrease and in cancer patients with distant metastases the serum level of AT III reduces.[19] There is only a few number of studies investigating the prognostic significance of AT III level. Bucheri et al. had reported 36% of their patients having reduced AT III level but low level of AT III was not determined as predicting poor prognosis.[11] Kemkes et al. found AT III level normal in patients with lung cancer.[20] In our study, we also investigated the prognostic significance of AT III level in lung cancer, and we found short survival in patients with low level of AT III. Further studies are needed to investigate the prognostic significance of low AT III level in lung cancer.

As a conclusion, patients with lung cancer mostly have hemostatic abnormalities which worsen with the progression of disease. Thus in lung cancer high level of D-dimer and low AT III level are correlated with short survival predicting poor prognosis independently from the histopathological type and tumor stage.

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