387

FIBRINOLYTIC ACTIVITY IN MALIGNANCY. A. Aranda, J.A. Páramo, B. Cuesta, J. Fernández, M.J. Paloma and E. Rocha. Hematology Service. University Clinic. University of Navarra. Pamplona. Spain.

Euglobulin lysis time (ELT), euglobulin fibrinolytic activity on fibrin plate (EFA), plasminogen, tissue-type plasminogen activator (t-PA) activity and antigen, α_2-antiplasmin (α_2-AP), plasminogen activator inhibitor (PAI) and fibrinogen degradation products (FDP) were determined in a group of 149 patients (mean age 57 ± 13 years, 93 male), with different malignancies (digestive 61, lung 18, urological 24, ginaecological 16, others 30). Findings were compared with those of 44 age-sex matched healthy subjects. There was a significant prolongation of ELT ($p < 0.003$), a decrease of plasminogen ($p < 0.004$) and an increase of PAI ($p < 0.0001$) in patients as compared to controls, being similar EFA, t-PA, α_2-AP and FDP. No differences in any ot these parameters were found in patients with metastatic disease (n= 65) as compared with those with local disease (n= 84). As regards to tumour localization, plasminogen and t-PA decrease were more pronounced in lung malignancies and PAI increase in lung and digestive malignancies. We conclude that there is an impairment in blood fibrinolytic activity in malignancy. Reduced fibrinolysis seems to be related to localization but not to degree of tumoral activity. That might have clinical complications.

388

THE INFLUENCE OF CHEMOTHERAPY ON THE PLASMATIC COAGULATION AND FIBRINOLYTIC SYSTEM IN LUNG CANCER PATIENTS. Ruiz,M.A.(1); Marugán,I.(1); Estellés,A.(2); España,F.(2); Aznar,J.(2); García-Conde,J.(1). Hospital Clínico Universitario Valèncía,Spain (1). Hospital La Fé, Valèncía. Spain (2).

Following the administration of cytostatic drugs, an increase in thromboembolic phenomena has been described in cancer patients. Such hemostatic alterations may be related to degree of hipercoagulability observed following chemotherapy, in comparison to previous levels. In terms of the fibrinolytic system, however, no -- clearly defined alterations have been detected. We studied the -- changes in plasmatic coagulation and fibrinolysis in 40 patients with non-operable stage III and IV lung cancer (30 epidermoid -- ad 10 microcytic neoplasms) following cytostatic chemotherapy. Two studies were done on each patient, i.e., one at the time of diagnosis, and the other 48 hours after completing the first chemotherapeutic cycle. The results show significant (p 0,05) post-chemotherapy increases in fibrinopeptide A (FPA) levels (pre: 2.95 ± 3.98, post: 8.15 ± 9.40 ng/ml), as well as a decrease in fibrinolytic activity reflected by a drop (p 0.01) in functional tissue plasminogen activator (t-PA) (pre: 1.53 ± 1.66, post: 0.91 ± 0.95 ng/ml). Morever, a tendency towards reduced euglobulinic precipitate lysis on fibrin agar was observed (pre: 122.8 ± 85.7, post: 105 ± 71.5%). The other parameters evaluated, i.e., antithrombin III, plasminogen immunologic t-PA and functional PA inhibitor -- (PAI) showed no significant changes.

We have also studied the potential accumulative effect of three chemotherapy courses and the results were compared to the situation at the time of diagnosis. A significant increase p 0.01 in functional PAI has been observed (pre: 1.85 ± 2.38, post: 5.41 ± 3.74 U/ml). The possible participation of tumor mass in the elevation of these parameter was considered: but no relation betwen tumor mass and increase PAI have been detected.

Chemotherapy is apparently capable of conditioning a decrease in fibrinolytic activity in these cancer patients, this could be related to the enhanced tendency of these patients to developing -- thromboembolic phenomena following cytostatic chemotherapy.

389

ALTERATIONS IN COAGULATION AND FIBRINOLYSIS IN LUNG CANCER PATIENTS. Ruiz,M.A.(1), Estellés,A.(2),Marugán,I.(1), Navarro,I.(1), Aznar,J.(2), García-Conde,J.(1). Hospital Clínico Universitario Valèncía, Spain (1). Hospital La Fé de Valèncía, Spain (2).

Lung cancer has commonly been associated with to both clinical problems of thromboembolism and to biological alterations in - coagulation and fibrinolysis.

We evaluated some coagulation and fibrinolytic parameters of the plasmatic coagulation and fibrinolytic system (Fibrinopeptide A (-FPA-) for enzimoimmunoassay, immunological tissue plasminogen activator (t-PA) for enzimoimmunoassay, functional (t-PA) for - chromogenic substrate and functional t-PAinhibitor (PAI) in 40 non-operable lung cancer patients (Table I) comprising 39 males and one female, aged 45 to 67 (average 59). The results are compared with those from a control group of 20 healthy male volunters aged 32 to 58 (average 48).

TABLE I

40 non-operable lung cancer patients (NLC).
26 local gross extension (NLGE)
22 stage III epidermoid
4 microcytic (situated within the thorax)
14 metastatic (NLM)
8 stage IV epidermoid
6 microcytic (extensive to outside the thorax)

Table II shows the results obtained (mean ± SD) for the parameters found to be significantly different to those of the control group. An increase is seen in the levels of FPA, functional t-PA and PAI in the lung cancer group. In the case of the extensive - lung tumor patients, FPAfpa and t-PA levels are significantly higher than for the group of locally advanced neoplasmas.

TABLE II

	Control	NLC	NLGE	NLM
FPA (ng/ml)	0.55±0.29	2.95±3.98•	2.43±5.28•	3.96±5.27••
Imm t-PA (ng/ml)	10.09±2.30	13.67±3.98•	14.12±4.34•	13.43±5.70•
Funct t-PA(ng/ml)	0.37±0.14	1.53±1.66•	0.97±0.67•	1.93±1.17••
PAI U/ml	0.38±0.34	1.68±1.97•	1.53±1.94•	2.01±2.04•

• $p < 0.05$ vs Control •• $p < 0.05$ NLM vs NLGE

The plasma of lung cancer patients therefore shows fibrinolytic alterations and an increase in thromboplastin activity.

390

TUMOR-ASSOCIATED FIBRINOLYSIS IN OVARIAN CARCINOMA - HPLC AND N-TERMINAL AMINO ACID ANALYSIS REVEAL THE PATHWAY OF DEGRADATION OF CROSSLINKED FIBRIN. O. Wilhelm (1), A. Henschen (2), R. Hafter (1) and H. Graeff (1). Frauenklink der Technischen Universität München (1) and Max-Planck-Institute for Biochemistry, Martinsried/Munich (2), FRG.

Crosslinked fibrin has been demonstrated by immunohistochemical tests to occur around tumor plugs, on the surface and in the stroma of the tumor in ovarian cancer. High levels of D-Dimer (200-800µg/ml), the characteristic terminal degradation product of crosslinked fibrin, are found in ascitic fluid of patients with advanced ovarian cancer. These findings suggest that fibrin polymerisation and degradation are related to and even may influence tumor growth. The kind of proteases which are responsible for degradation of crosslinked fibrin is, however, unknown.It was the aim of this study to evaluate whether plasmin and/or other proteases are involved in tumor-associated fibrinolysis. Therefore the total high-molecular-weight fibrin degradation products in ascitic fluid were purified by protamine sulfate precipitation, gel filtration, immunoadsorption and compared with the components of plasmin-degraded crosslinked fibrin, i.e. DD,DY,YX,DXD and DXY, by direct SDS-PAGE in the absence of mercaptoethanol and after excision of the bands, mercaptolysis and re-electrophoresis. Pronounced similarity between the two sets of fragments was observed. For further information the fragments from the two sources were mercaptolysed and their polypeptide chain components separated by reversed-phase high-performance liquid chromatography, the components being identified by N-terminal sequence analysis and SDS-PAGE. Highly similar patterns were obtained and components corresponding to γ-γ , γ-γ^1, β , β^2 and α^1could be recognized. The findings provide strong evidence for plasmin being the primary protease involved in ovarian carcinoma-related fibrinolysis.

(supported by Deutsche Forschungsgemeinschaft,SFB 207,A2).