ONCOLOGY

DISTURBANCE OF ANTITHROMBOGENIC ACTIVITY OF THE VESSEL WALL IN MALIGNANCY

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Growth of a malignant tumor can have a definite effect on hemostasis and, in turn, the hemostasis system may affect growth of the tumor [9]. It has been shown that the blood vessel wall is a regulator of the hemostasis system, and antithrombin III, the main anticoagulant of the blood, prostacyclin, a powerful endogenous inhibitor of platelet aggregation and a vasodilator, and plasminogen activator are synthesized in it. Reduction of synthesis and release of regulators of the hemostasis system into the blood stream leads to enhancement of the thrombogenic potential of the blood, and to thrombotic disease [2, 8]. The response of tumor cells with the vessel wall and component of the hemostasis system plays the central role in metastasization [9, 13]. The lower the concentration of anticoagulants and prostacyclin in the blood, the greater the probability of interaction of the tumor cells with platelets and activation of the clotting system of the blood on the surface of the cells, leading to the formation of oncogenic—thrombogenic emboli, which may cause microembolism of the vessels of the microcirculatory system of different organs and may become foci of metastasization.

The aim of this investigation was to study the state of the antithrombogenic properties of the blood vessel wall in patients with tumors.

EXPERIMENTAL METHOD

Altogether 60 patients with carcinoma of the lung, stomach, and breast in the T_2-T_4 form were under observation. The total number was made up of 41 men and 19 women. Their ages were 41-60 years. Metastases in the lymph nodes were found in 38% of the patients. The investigation was carried out before treatment. The diagnosis was confirmed histologically. As the control, 30 clinically healthy men and women similar in their working and living conditions and diet to the patients, were investigated. To examine several additional problems experiments also were carried out on 60 male Wistar rats weighing 180-200 g, with a transplantable PA-2 rat tumor. The tumor was grafted in the region of the animals' thigh by a technique traditionally adopted in experimental oncology. The antiaggregating and anticoagulant activity of the vessel wall was determined by the method in [3, 4], the fibrinolytic activity of the vessel wall as in [7], and Willebrand factor as in [1]; the remaining parameters of the hemostasis system were determined by methods described in the textbook [6]. The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

As the data in Table 1 show, the anticoagulant and fibrinolytic activity of the blood of the patients with cancer was lower than in healthy individuals, the level of Willebrand factor in the blood was higher, and intravascular and spontaneous platelet aggregation was discovered. Table 1 shows that when the tourniquet test of antithrombogenic activity of the vessel wall was performed in a certain way, during temporary occlusion of the vessels of the forearm by the sphygmomanometer

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TABLE 1. Antithrombogenic Activity of Vessel Walls in Healthy Individuals and Cancer Patients (M ± m)

Parameter	Normal individuals	Patients	p
Antiaggregative activity:coagulation method, %			
Before compression	64,0±2,7	72,0±9,0	
After compression	40,0±3,0	65,0±8,0	
Index	1,5	1,1	<0,05
Anticoagulant activity: coagulation method, %			
Before compression	100,6±2,5	74,0±4,3	
After compression	128,0±3,8	78,0±5,2	
Index	1,28	1,05	<0,05
Fibrinolytic activity, %			
Before compression	30,0±3,9	23,0±4,6	
After compression	46,0±6,8	27,0±6,2	
Index	1,7	1,2	<0,05
Intravascular platelet aggregation, %			
Before compression	11,0±2,0	21,0±4,0	
After compression	6,0±2,1	20,0±5,0	<0,05
Spontaneous platelet aggregation, %	0,0	5,4±2,5	<0,05
Willebrand's factor, units/ml	1,32±0,04	2,20±0,09	<0,05

TABLE 2. State of Vaso-Thrombocytic Stage of the Hemostasis System in Rats with PA-2 Tumor (M ± m)

Experimental conditions	Control			
	ADP-induced platelet aggregation	index of intravascular aggregation	antiaggregative activity of vessels	anticoagulant activity of vessels
Control	39,0±2,4	1,4±0,1	32±0,54	16,2±1,7
Time after transplantation of tumor				
9	52±1,1*	3,4±0,3*	30±1,1	
15	74±4,7*	2,9±0,3	19±2,6*	
24	54±1,3*	2,2±0,2*	29±1,1*	12,7±0,9*
30		1,5±0,3	30±2,0	

Legend. *$p \leq 0.05$: results are significant.

cuff induced release of several antithrombogenic factors synthesized by the vessel wall in healthy individuals: prostacyclin, antithrombin III, and plasminogen activator. For instance, after the tourniquet test ADP-induced platelet aggregation fell on average by 37%, the blood antithrombin III level rose on average by 27%, and the fibrinolytic activity of the blood increased on average by 53%. By contrast, in patients with cancer, after the tourniquet test ADP-induced platelet aggregation on average remained unchanged, and in some patients it actually increased. The tourniquet test did not affect intravascular platelet aggregation, which remained high even after that test. In the patients the tourniquet test did not stimulate release of antithrombin III or plasminogen activator into the blood stream.

The results indicate marked inhibition of synthesis of prostacyclin, antithrombin III, and plasminogen activator and of their release into the blood stream in cancer patients. Reduction of the antithrombogenic activity of the vessel wall was observed equally in the presence of tumors in different locations. With differences in severity of the disease, the depth of the disturbances was the same as in atherosclerosis and ischemic heart disease [8].

The question arises whether the decrease in antithrombogenic activity of the vessel walls in cancer patients is a primary and pathognomonic sign of the disease, or whether it is secondary, a reduction to intravascular activation of the hemostasis system, induced by tumor growth, or, in some patients, in whom the disease was accompanied by atherosclerosis, the decrease was the result of an atherosclerotic lesion of the vessel walls.

As the results in Table 2 show, growth of a transplantable PA-2 tumor is accompanied by a decrease in the antithrombogenic (antiaggregative and anticoagulant) activity of the animals' vessel walls. In animals with tumors, ADP-induced platelet aggregation was enhanced during tumor growth and intravascular aggregation increased. These findings indicate an increase in sensitivity of the platelets of the animals with tumors to aggregation inducers.

It can be concluded from the results that the antithrombogenic activity of the vessel walls is depressed in cancer patients, leading to a disturbance of hemostatic homeostasis and to an increase in the thrombogenic potential of the blood, and it may be a stage in the pathogenesis of metastasization of a malignant tumor.

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