

## CLINICAL STUDY

## General changes in hemostasis in gastric cancer

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**Abstract:** Disorders of haemostasis and haemocoagulation are often seen in patients with cancer as a part of paraneoplastic syndrome. Thrombotic and/or haemorrhagic complications are the second most common cause of mortality in patients with cancer. The evaluation of the haemostatic parameters of 67 patients with gastric cancer have indicated tendency to thrombophilia and activation of intravascular coagulation, of which 31.3 % showed tendency to hypercoagulation and 47.8 % disseminated intravascular coagulation (DIC). Only 7.5 % of subjects have yielded normal laboratory findings while 5.9 % of patients had DIC with remarkable hypocoagulation. Thrombocytosis, platelet hyperaggregability and elevation of beta-thromboglobulin are the indicators of changes in primary haemostasis and elevation of thrombomodulin indicates vascular wall damage. Lower antithrombin III levels, C-protein and S-protein in plasma have indicated lower anti-thrombotic potential in patients with gastric cancer. It can be concluded that patients suffering from gastric cancer are at higher risk of thromboembolism as for haemorrhagic diathesis (20.1 % thromboembolism, 11.94 % fatal thromboembolic events vs 5.9 % haemorrhagic diathesis) (Tab. 5, Ref. 22). Full Text (Free, PDF) [www.bmj.sk](http://www.bmj.sk).

Key words: gastric cancer, primary hemostasis, fibrinolytic system, thromboembolism.

The increased number of thrombotic as well as haemorrhagic symptoms in oncologic patients represents a severe complication very often directly threatening their lives. Haemostatic changes can therefore decisively influence the course and prognosis of malignant diseases. The complex anti-tumour therapy is based on early disclosure of tumour, as well as on the initiation of systematic prophylaxis and therapy. The problem of haemostatic changes is best described in hematologic malignancies, only several studies deal with this problem in association with solid tumours. The aim of this study was to identify the presence of paraneoplastic syndrome in patients with gastric carcinoma.

**Judgement of general changes in hemostasis** We have chosen gastric cancer to be our model. We were interested in the fact whether in patients suffering from gastric cancer or precancer the gastric acid per se contains substances capable of activating or inhibiting the system of hemostasis. Systemic changes in hemostasis can reflect the risk of thromboembolic complications. It was our endeavour to find out whether they involve the changes of primary hemostasis, hemocoagulation, inhibitors of coagulation or fibrinolysis. Based on this knowledge, it would be possible to choose optimal therapeutic or preventive procedures.

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**Patients, material and methods***Overall changes in blood clotting in patients with gastric carcinoma*

Overall, we have examined 132 patients forming two groups. The first group was comprised of 67 patients with gastric cancer (35 males and 32 females) at age ranging from 29 to 92 years (median 67 and 95 % CI ranging from 59 to 71). The diagnosis was verified by gastrofiberscopy, as well as histologically, or confirmed by surgical or post mortem findings. Based on histologic examination, the group was formed by 47 patients with variously differentiated gastric carcinomas, 8 patients suffered from sigilocellular carcinomas, 4 from mucoid carcinomas, 1 patient has gastric leiomyoma, 2 patient were after surgical procedure duo to sigilocellular gastric carcinoma, 1 patient had gastric reoccurring adenocarcinoma, in 3 patients stomach adenocarcinomas were diagnosed after the resection of stomach according to Billroth II for gastric ulcers, and 1 patient had sigilocellular carcinoma within his stomach found following its resection due to ulcers.

The control group was composed of 65 people, 32 males and 33 females at age ranging from 17 to 74 (median 37 and 95 % CI in range from 33 to 38).

The examination of hemostasis consisted of a whole complex of laboratory tests presented below.

*Primary hemostasis*

The judgement of primary hemostasis changes was based on the parameters:

*Thrombocytes (Tr)* the count of thrombocytes was automatically assessed by means of multiparameter counter of blood cells SYSMEX CC780 (TOA, Japan).

*Aggregation of thrombocytes* – native aggregation of thrombocytes (NAT) and aggregation of thrombocytes induced by adrenalin (IAT), the aggregation of thrombocytes was investigated by microscopic examination of whole-blood samples by Valaskara nad Chilte

*Betathromboglobulin (BTG)* was assessed by means of radio-immunologic commercial kit of Radiochemical Centre (Amersham, England).

*Thrombomodulin (TM)* was examined by ELISA method, by means of Asserachrom Thrombomodulin diagnostic kit, DIAGNOSTICA STAGO (France).

#### *Examination of plasmatic hemocoagulation system*

*Prothrombin time (PT)* the activities of prothrombin complex factors (according to Quick) were assessed by means of commercial NEOPLASTINE CI PLUS, DIAGNOSTIC STAGO test (France) by FIBRINTIMER, LABOR COA DATA 1000 apparatus (Germany).

**Activated partial thromboplastin time (APTT)** was assessed by means of the PTT-LA, DIAGNOSTICA STAGO kit (France) and using the FIBRINTIMER, LABOR COA DATA 1000 apparatus (Germany).

*Thrombin Time (TT)* was assessed by means of a procedure described by Sakalová a Lipšis et al (1995).

*Fibrinogen (Fbg)* the level of fibrinogen was assessed nephelometrically by immunoprecipitation method using the commercial kit FIBRINOGEN, DIAGNOSTICA ORION and by means of TURBOX, DIAGNOSTICA ORION apparatus (Espoo, Finland).

**Fibrin monomers (FM)** we assessed them immunologically by means of the F.S. TEST, DIAGNOSTICA STAGO (France).

#### *Natural inhibitors of blood clotting*

*Antithrombin III (ATIII)* the assessment of the antigen of antithrombin III (AT III ag.) was done by using the immunoprecipitation method by means of the AT III test, DIAGNOSTICA ORION, (Espoo, Finland). The assessment of biologic activity of antithrombin III /AT III ac) was done photocolometrically and based on the principle of chromogenic substrates, by means of the STACHROM AT III kit, DIAGNOSTICA STAGO (France).

*Protein C (PC)* – antigen was assessed by ELISA method, by using the commercial ASSERACHROM PROTEIN C kit, DIAGNOSTICA STAGO (France).

*Protein S (PS)* – antigen of the total protein S was assessed by ELISA method by means of the commercial ASSERACHROM TOTAL PROTEIN S kit, DIAGNOSTICA STAGO (France). Antigen of the free protein S was assessed by ELISA method by means of the commercial FREE PROTEIN S kit, DIAGNOSTICA STAGO (France).

#### *Fibrinolytic system*

*Lysis of euglobulins (LE)* the fibrinolytic activity of plasma was assessed by the method of lysis of euglobulins according to

Kowarzyk and Buluk. The results were recorded as the point of final lysis of fibrin coagulum.

*Plasminogen (Plg)* the assessment of the activity of plasminogen was done photocolometrically and based on the principle of chromogenic substrates with the use of STACHROM PLASMINGEN tests, DIAGNOSTICA STAGO (France).

*Degradation products of fibrin (Ddi)* were assessed by semi-quantitative latex agglutination method by means of Ddi TEST kit, DIAGNOSTICA STAGO (France).

#### *Statistical methods*

The investigated indicators were characterised by means of medians, their 95 % confidential intervals and we assessed the upper and lower quartiles. When processing the quantitative indicators of the overall blood clotting, the differences between individual indicators in the group of gastric carcinoma when compared with the control group were judged by means of non-parametric test according to Mann Whitney. Results: Systematic changes in hemostasis.

## **Results**

#### *Systemic changes in hemostasis*

The further part of evaluation dealt with detecting the changes in individual laboratory parameters of the overall blood clotting in patients with gastric carcinomas when compared with the control group.

#### *Primary hemostasis*

Thrombocytes in amount of 112 to 382 G/l, (median 192; 95 % CI 188–200) were detected in the control group and in patients with gastric carcinomas the values ranged from 28 to 830 G/l (median 274, 95 % CI 239–297). When evaluating the whole group of patients with cancer and when comparing them with the control group we did not find any statistically significantly higher counts of thrombocytes ( $p < 0.001$ ). The values of native aggregation of thrombocytes in the control group ranged from 0 to 8% (median 4, 95 % CI 4–6), in patients with cancer they extended from 2 to 38 % (median 12, 95 % CI 9–15). In patients with cancer their values were significantly higher ( $p < 0.001$ ). In patients with cancer, values were significantly increased also in aggregation of thrombocytes induced by adrenalin ( $p < 0.001$ ): in the control group its values were ranging from 4 to 36 % (median 12, 95 % CI 10–12), in patients with cancer they extended from 4 to 56 % (median 33, 95 % CI 28–38). The values of beta-thromboglobulin in the control group ranged from 16 to 116 ng/l (median 59, 95 % CI 34–84), in the group with cancer from 24 to 300 ng/l (median 162, 95 % CI 96–180). In patients with cancer it was significantly higher ( $p < 0.001$ ).

The values of thrombomodulin in the control group ranged from 12.3 to 45.95  $\mu\text{g/l}$  (median 25.3, 95 % CI 20, 3–34.2) and in the group with cancer from 21.7 to 134  $\mu\text{g/l}$  (median 49, 95 % CI 39.9–56.1). In patients with gastric cancer a significant increase in the level of thrombomodulin was found in plasma ( $p < 0.001$ ). The Table 1 reviews the results of examinations of

**Tab. 1. Primary hemostasis results in individual groups.**

Parameter	Control group	Gastric cancer
Count of thrombocytes (g/l)	192 (176–219) [188–200]	274*** (206–410) [239–297]
Native - Initial aggregation of thrombocytes (%)	4 (4–6) [4–6]	12*** (7–17) [9–15]
Aggregation of thrombocytes after the induction by adrenalin (%)	12 (8–14) [10–12]	33*** (21–42) [28–38]
Betathromboglobulin ng/l	59 (32–86.5) [34–84]	162*** (96–187) [96–180]
Thrombomodulin µg/l	25.3 (19.8–35.5) [20.3–34.2]	49*** (36.8–60.5) [39.9–56.1]

Presented are medians (upper and lower quartiles): [95 % Confidential Intervals], \*\*\* = p<0.001

**Tab. 2. Review of basic coagulation test results in individual groups.**

Parameter	Control group	Gastric cancer
Prothrombin time, activity of prothrombin complex factors (%)	96.1 (92.5–101) [95–99]	90** (80–100) [84.4–94]
Activated partial thromboplastin time (s)	35.1 (33.6–36.9) [34.4–36.9]	37.5 (34.9–42) [35.9–40]
Thrombin time (s)	18.8 (17.5–20.9) [18.3–19.9]	19.4 (18–26) [18.5–22]
Fibrinogen (g/l)	2.2 (1.95–2.45) [2–2.36]	4.3*** (3–4.8) [3–4.8]

Presented are medians (upper and lower quartiles): [95 % Confidential Intervals], \*\* = p<0.001, \*\*\* = p<0.001

the primary hemostasis, median, upper and lower quartiles and 95 % CI of individual indicators.

#### Hemocoagulation system

When judging the coagulation potential of plasma in the whole group of patients with gastric cancer and comparing it with the control group we have detected a lower activity of the factors of prothrombin complex (p<0.01). In the control group the values were ranging from 75 % to 133 % (median 96.1, 95 % CI 95–99), while in patients with cancer from 30 % to 123.4 % (median 90, 95 % CI 84.4–94). When compared to the control group, in the group with gastric cancer we revealed a prolongation of the activated partial thromboplastin time (p<0.001). The APTT value in the control group was ranging from 29 to 50 s

(median 35.1, 95 % CI 34, 4–36.9) and in patients with cancer from 23.5 to 400 s (median 37.5, 95 % CI 35, 9–40). We have detected no statistical differences in values of thrombin time. In the control group its values were ranging from 15.3 to 32.9 s (median 18.8, 95 % CI 18.3–19.9) and in patients with gastric cancer from 14 to 400 s (median 19.4, 95 % CI 18.5–22). The values of fibrinogen were in the whole group of patients with gastric cancer significantly increased when compared to the control group (p<0.001). Its values in the control group were ranging from 1.2 to 4.9 g/l (median 2.2, 95 % CI 2–2,6), in patients with gastric cancer we however detected an extremely wide dissemination of values ranging from 0.21 to 8.2 g/l (median 4.3, 95 % CI 3–4.8); Fibrinogen values below 1 g/l being a hemostatically safe level was detected in two patients. The Table 2 reviews the results of coagulation potential of plasma in individual groups. The presence of monomers of fibrin in plasma was detected in 14 (25 %) patients out of 65 examined in the group with gastric cancer and in no member of the control group.

#### Blood clotting inhibitors

When evaluating the results of natural inhibitors of blood clotting we detected a statistically decreased value of the anti-thrombin III antigen in the group with gastric cancer when compared to the control group (p<0.001). The AT III values in the control group were ranging from 0.19 to 0.43 g/l (median 0.29, 95 % CI 0, 27–0.3) in the group with gastric cancer from 0.1 to 0.32 g/l (median 0.23, 95 % CI 0, 2–0.24). The median of AT III activity in the group suffering from gastric cancer was 95 % (95 % CI 81.8–101), in the control group the median was 86.9 % (95 % CI 86–91.3), this difference was not statistically significant. In patients with cancer we detected a wide dissemination of values, with the finding of both, very high and very low levels of AT III from 24.8 % to 150 %, while in the control group this range was from 59.9 % to 125 %.

The values of protein C antigen in the group with gastric cancer (median 82.2 %, 95 % CI 71.5–91.4 %) when compared to the control group (median 98.6 %, 95 % CI 96.4–103.9 %) were statistically significantly lower (p<0.001). The range of values in the group with gastric cancer (34.6–155 %) was again higher than in the control group (64.8–127.6 %). When comparing the results of total protein S in the group with gastric cancer with the control group we detected that the values in patients with cancer were lower. However this difference was almost at the boundary of statistical significance (p=0.05). The values in the control group were ranging from 58.5 to 106 % (median 85.4, 95 % CI 79.2–90.6) and in the group with cancer from 70 to 89.8 % (median 78.6, 95 % CI 71.2–84.4). The decrease in the values of free protein S antigen in patients suffering from cancer (median 81.2 %, 95 % CI 72–88.4 %) when compared to the control group (median 87.6 %, 95 % CI 80–96.9 %) was statistically significant (p<0.05). The ranges of values in both groups were similar, namely 58.8 to 113 % in the control group and 58.2 to 97.4 % in gastric cancer. The values of blood clotting inhibitors in individual groups are reviewed in Table 3.

**Tab. 3. Values of blood clotting inhibitors in individual groups.**

Parameter	Control group	Gastric cancer
Antithrombin III - antigen g/l	0.29 (0.27–0.31) [0.27–0.3]	0.23*** (0.17–0.26) [0.2–0.24]
Antithrombin III - activity %	86.9 (79.6–93.4) [86–91.3]	9 (68.1–113) [81.8–101]
Protein C - antigen %	98.6 (87.3–105) [96.4–103.9]	82.2*** (61.5–93.8) [71.5–91.4]
Total Protein S - antigen %	85.4 (79.1–90.9) [79.2–90.6]	78.6 (75–80.4) [71.2–84.4]
Free Protein S - antigen %	87.6 (79.8–100) [80–96.9]	81.2* (72–88.4) [72–88.4]

Presented are medians (upper and lower quartiles); [95 % Confidential Intervals], \* =  $p < 0.005$ , \*\*\* =  $p < 0.001$

**Tab. 4. Values of blood fibrinolytic parameters in the control group and in the group of gastric cancer.**

Parameter	Control group	Gastric cancer
Euglobulin Lysis (minutes)	390 (300–460) [360–420]	260*** (233–305) [240–300]
Plasminogen (%)	88 (81.5–94) [87–93]	89 (77–104) [78–98]

Presented are medians (upper and lower quartiles), [95 % Confidential Intervals], \*\*\* =  $p < 0.001$

#### Fibrinolytic system

The median of lysis of euglobulins in both groups was over the lower limit of standard (240), the comparison of our groups has shown that in patients suffering from cancer the dissolution of coagulum was quicker (median 260 min, 95 % CI 240–300 min) than in the control group (median 390 min, 95 % CI 360–420 min;  $p < 0.001$ ). In the group with cancer we also detected extremely short times of lysis of euglobulins (the values ranged from 15 to 400 min), whereas in the control group the values ranged from 160 to 600 minutes.

The median of plasminogen level in the group with cancer 89 % (95 % CI 78–98 %) did not significantly differ from the values of the control group 88 %, 95 % CI 87–93 %. In the group with cancer we also detected extremely low plasminogen level (the values ranged from 15 to 135 %), in the control group the values ranged from 69 to 145.8 %. The levels of indicators of fibrinolytic activity of blood are presented in Table 4.

When compared with the control group, the plasma of patients with gastric cancer was detected to contain a significantly increased amount of fibrin degradation products Ddi ( $p < 0.001$ ). Table 5 reviews the Ddi results in individual groups. In the con-

**Tab. 5. Values of D dimers (D/di) in control group and group of gastric cancer.**

Ddimer	Control group	Gastric cancer
Negative	65	35
+	0	19
++	0	13

Negative =  $< 500$  ng/l, positive (+) =  $> 500$  ng/l, strongly positive (++) =  $> 1000$  ng/l  $\chi^2 = 40.97$ ; free degree of 2,  $p > 0.001$

trol group we found no positiveness of Ddimer in plasma; in 32 out of 67 (47.8 %) patients with cancer Ddimer was positive ( $p < 0.001$ ). In 13 patients, the Ddimer was proven to be strongly positive (concentration  $> 1000$  ng/l).

#### Complete examination

Based on the current evaluation of all examined laboratory indicators of hemocoagulation and hemostasis we judged the complex laboratory picture in 67 patients with gastric cancer; the findings were classified as follows:

- 1) Normal laboratory findings were in 5 patients (7.5 %)
- 2) Thrombocytopenia (due to metastases in bone marrow) was found in 1 patient (1.5 %)
- 3) Hypercoagulation state was found in 20 patients (31.3 %); herein were included patients with increased thrombocytic counts and aggregation of thrombocytes, increased coagulability of plasma, increased level of fibrinogen and normal or decreased AT III levels.
- 4) Compensated activation of hemostatic system was found in 32 patients (47.8 %), in whom the hypercoagulability was shifted into the activation of disseminated intravascular blood clotting (DIC) with the presence of FM, fibrin degradation products (Ddi) within circulation, shortened PT as a manifestation of compensation of the increased synthesis of coagulation factors at their slow consumption, normal or moderately increased AT III with normal or increased thrombocytes.

5) Hypercoagulation state affected by therapy. In two patients (3 %) the anticoagulation therapy (Pelentan) together with antithrombotic therapy (Fraxiparin) due to acute phlebotrombosis was commenced prior to the examination. However, at the time of the examination the laboratory pictures did not yet reflect the therapy and still yielded the signs of hypercoagulation.

6) Fully advanced DIC syndrome with consumption coagulopathy. In 4 patients (5.9 %) it was connected with severe hypo-coagulation. In one patient the consumption coagulopathy was the first manifestation of tumour disease and in three patients it was detected in the generalised stage of tumour disease. In this group, a marked increase in Fbg level was detected (0.2–0.9 g/l), as well as strongly positive Ddimer, a decrease in the level of thrombocytes, AT III, C and S proteins, prolonged Pt and APTT.

7) Decreased activity of prothrombin complex factor, fibrinogen, antithrombin III (malnutrition, liver metastases) were present in two patients (3 %).

### Clinical picture

Obvious clinical manifestations of hemostatic disorders in patients with gastric cancer have occurred in 18 out of 67 patients (26.8 %). Five patients had phlebothrombosis, two after the diagnosis of carcinoma; in three of them it preceded for several years the diagnosis of the neoplastic process. In one patient, terminal thrombosis of the superior mesenteric artery occurred with the clinical picture of ileum due to sigilocellular carcinoma. Six patients died due to massive embolisation into the pulmonary artery, one patient died due to acute myocardial infarction confirmed by post mortem finding. In four patients an advanced consumption coagulopathy occurred accompanied by hemorrhagic diathesis, in one of them it was the first manifestation of a small stomach adenocarcinoma found as late as at necropsy. In another, it was the cause of death due to generalised adenocarcinoma with multiple metastases in abdominal organs and lungs. Multiple manifestations of thromboembolic complications were present in a patient who at the age of 34 overcame myocardial infarction, later had reoccurring phlebothromboses of lower limbs with pulmonary embolisation, due to which he was administered pelentan. At the age of 35 he was diagnosed to suffer from an inoperable gastric carcinoma. In six patients, several years prior to the finding of gastric carcinoma, there was a record of myocardial infarction, while in three of them the myocardial infarction reoccurred.

### Discussion

In compliance with the studies of other authors, our results have proved that in tumour diseases the laboratory disorders of hemostasis are frequent and the clinical manifestations are variable. Despite the fact that the occurrence of hemostatic changes is especially high in generalised tumours simultaneously afflicting several components, severe changes with significant clinical findings were detected also in very small non-metastasising tumours. According to case histories of some patients, the clinical manifestations of thrombosis had preceded the diagnosis of the tumour disease by several years. After having evaluated the wide scale of laboratory tests of overall hemostasis we can state that only 7.5 % of our group of patients with gastric carcinoma were negative in all tests. This fact corresponds with literature data, namely that as many as 95% of patients with cancer have at least one test proving the activation of hemostasis to be abnormal (1). In 90 % of patients with cancer Gouin and Sammam (2) describe changes in routine laboratory tests proving hypercoagulability. Most frequent are the thrombocytosis, increase in coagulation factors, fibrinogen and degradation products of fibrinogen and fibrin (3, 4). In our set of patients with gastric cancer, we detected laboratory changes on all levels (primary hemostasis, coagulation factors, fibrinolysis, and coagulation inhibition). The plasmatic increase in thrombomodulin in our set of patients with gastric cancer indicates that endothelium has been impaired. The impairment can be transient or permanent and vary as to its type. The finding of increased thrombomodulin can coincide with neovascularization, penetration of tumour cells into

the metastatic cascade. Even the release of thrombomodulin from tumour cells cannot be excluded as some observations indicate that during their transformation tumour cells can gain the ability to synthesize thrombomodulin (5). Finally, thrombomodulin increased in the plasma of patients with cancer can be brought on by its splitting off the membrane of endothelial cells since in these patients an increase in the number of proteolytic enzymes is detected (6, 7). A correlation between the increase in thrombomodulin and the metastatic spread has been observed in patients with squamous pulmonary carcinoma (8).

The changes in primary hemostasis are indicated by the fact of the reactive increase in the number of thrombocytes, the fact of which we observed in 29 patients (43.3 %); in part of them the increase could have been caused by bleeding. Increased levels of native aggregation of thrombocytes and betathromboglobulin indicate to their *in vivo* reactivity. The high percentage of adrenalin-induced thrombocytic aggregates in patients suffering from cancer indicates that their *in vitro* reactivity is also high when compared to the control group. Thrombocytes activated by means of changes in the spreading of membranous phospholipids represent the active surface of coagulation system. They are more adhesive. This is why they can contribute to the dissemination of tumour. Our findings are in agreement with literature data, according to which 30–60 % of patients with advanced tumour disease have abnormalities in the quantity and quality of thrombocytes being similar to those observed in our set (9). Several studies have gathered the evidence supporting the conception that the ability of tumour cells to induce the aggregation of thrombocytes correlates with their metastatic potential (10, 11). Despite the latter fact, the literature data on the use of anti-platelet drugs as inhibitors of metastasising are controversial (12).

A great part of patients suffering from gastric cancer (34.51 %) were observed to increase their levels of fibrinogen significantly. In majority of them, the high level of fibrinogen is a manifestation of hypercoagulation state, most probably entailed by the acute-phase reaction. In part of patients with hyperfibrinogenemia, the positiveness of Ddimer signifies that the activation of hemostatic system has already been compensated. Fibrinogen, more than other plasmatic proteins, contributes to blood viscosity; it is a factor determining the rheological properties of blood. The increased viscosity of blood together with its disturbed microcirculation can be the factor co-operating in the activation of hemostatic mechanisms in patients with cancer. The lack of effective anticoagulation system can also contribute to abnormal blood clotting in tumour diseases.

When judging the group of patients with gastric cancer by comparing it to the control group we found a statistically significant decrease in the antigen of antithrombin III; however the change in the level of AT III was not statistically significant. In 14 patients (21 %) however, we found extremely low values of AT III activity (24–68 %), together with low values of AT III antigen (0.1–0.17 g/l). This is in compliance with our previous observation that both methods of AT III examination correlate (13). Regarding the fact that the ATIII level is not affected by liver metastases, we assume its consumption in DIC.

The decrease in anti-coagulation ability of plasma is indicated also by the decrease in the levels of other natural inhibitors of blood clotting as C and S proteins. In our set of patients with gastric cancer we found statistically decreased values of PC antigen and free PS antigen. The decrease in the level of antigen of total S protein was on the border of statistical significance. The increased coagulation activity in malignant diseases can thus be brought on by the insufficiency of one or several anticoagulation proteins, as ATIII, C and S. It is known that cancer cells can release a number of various types of proteolytic enzymes. These proteinases can activate the hemostatic system and induce the gained decrease in the activity of protein C as a result of consumption. Significant hypercoagulability can be preceded by the increase in both number and reactivity of thrombocytes, impairment of the contiguous endothelial layer, entrance of tumour cells and procoagulant substances produced by tumour cells into the intravascular space, increase in viscosity, changes in blood flow and disorders in anti-coagulation systems. The presence of fibrin-degradation products in 47.8 % of our set of patients signifies that hypercoagulation was escalated to the extent of disseminated intravascular blood clotting and subsequent fibrinolysis. Various degrees of activation of hemostatic system and DIC were associated also with the changes found in prothrombin time and activated partial thromboplastin time. The hypercoagulation state and compensated DIC was found to have both PT and APTT shortened, and in patients with consumption coagulopathy both tests were prolonged markedly. The patients with consumption coagulopathy were observed to have hypofibrinogenemia at average values of 0.33 g/l (values ranging from 0.2 to 0.45 g/l) and increased fibrinolysis. It is to be noted however, that the result of fibrinolysis measured by the test of lysis of euglobulins is significantly influenced by the starting level of fibrinogen, thus the real extent of activation of the fibrinolytic system cannot be evaluated. Moreover, also the level of plasminogen in patients with consumption coagulopathy was markedly lowered with the average value of 27.6 % (ranging from 15 to 41 %). This fact on one hand proves the activation of fibrinolysis to be marked, but at the time of our examination the fibrinolytic potential might have been exhausted as a result of its consumption during the DIC process. When evaluating the results of lysis of euglobulins in the whole group of our patients with carcinoma we found out that the time had been shortened (median 260 minutes) when compared to the control group (median 290 minutes). Especially the causes of increased fibrinolysis in patients with consumption coagulopathy might have contributed to the statistical significance of this difference. In reality, the patients with no consumption coagulopathy yielded the time of lysis of euglobulins in the normal range of values. When compared to previous observations (14, 15), in the whole group of our patients we have not proved any decrease in fibrinolysis.

Our results indicate that patients with gastric carcinoma yield thrombophilia and therefore are at risk of thromboembolic complications. In compliance with the studies of other authors we have detected subclinical activation of intravascular blood clotting in a large number of patients already prior to the commencement of therapy (2, 4). Chemotherapy and surgery further in-

crease the risk of thromboembolic complications. Nowadays, there are safe and effective prophylactic methods (low-molecular heparins, antiaggregatory and anticoagulatory therapies). Therefore, there is a need of sensitive tests for the detection of the hypercoagulation state in order to avoid thromboembolic complications. The results of our laboratory examinations showed that only 7.5 % of patients with gastric cancer yielded normal hemostatic findings. As many as 82.1 % of patients had a prothrombotic predisposition determined by hypercoagulation or compensated activation of hemostatic system. These laboratory changes thus correspond with chronic activation of hemostatic system caused by the permanent presence of the activating stimulus of a relatively low intensity. According to literature data, clinical manifestations of venous thromboembolism or bleeding are present in 9–15 % of patients with malignant diseases (16, 17). In our set of patients we have observed thromboembolic complications in as many as 18 out of 67 patients (26.8 %). Six patients developed massive pulmonary embolisation being the proximate cause of death, and one patient developed fatally extensive myocardial infarction. Literature presents also contradictory reports relating to profound venous thrombosis and tumour disease. It has been shown that as many as 10–20 % of individuals suffering from idiopathic profound venous thrombosis while lacking the generally known risk factors of thrombosis have a probability of tumour disease (18, 19). Only in 4 of the patients (5.9 %) we have detected the acute form of DIC with fully developed picture of consumption coagulopathy and clinical manifestation of bleeding. In three of them this complication was manifested in the terminal stage of the disease; in one of them it was the first manifestation of a small stomach adenocarcinoma, which was detected as late as at necropsy. Our clinical observations imply that patients with gastric cancer are more exposed to the risk of thromboembolism than to that of hemorrhagic diathesis. A relatively large percentage of patients with thromboembolic complications in our set and especially the severity of these complications bring on the question of the necessity of preventive antithrombotic therapy in these patients. Literature provides ambiguous reports on the effect of anticoagulation therapy by means of Warfarin rather in association with tumour diseases of other origin (lung, breast, ovary). Kakkar et al (20) present that also the use of LMWH can reduce mortality in gastric cancer. The authors recommend the administration of preventive antithrombotic therapy during active disease (21, 22). Also our results support the urgent necessity of this therapy, especially when excluding other risks of anticoagulation therapy.

## Conclusion

Based on our complex evaluation of a wide range of laboratory indicators of hemostasis, the clinical state of our patients as well as on the compliance with the studies of other authors we can state that laboratory disorders of hemostasis in gastric cancer are frequent and variable. The disorders that can possibly be involved are those of primary hemostasis, hemocoagulation, fibrinolysis or coagulation inhibitors.

1) The observed staging of coagulation processes taking place with no clinical symptoms was observed more frequently than the hypocoagulation of blood.

2) The high occurrence of laboratory changes in hemostasis was observed in generalised tumours with only several components changed.

3) The reactive increase in the count of thrombocytes, the increase in the aggregability of thrombocytes as well as the increase in the level of beta thromboglobulin accompanied by the increase in the level of thrombomodulin indicate a change in primary hemostasis.

4) The hypercoagulation in one half of our patients was observed to be escalated into the activation of disseminated intravascular blood clotting and subsequent fibrinolysis. The subclinical activation of intravascular blood clotting was observed in a large amount of patients already prior to therapy.

5) Our clinical observations imply that in patients with gastric cancer the risk of thromboembolism is greater than that of hemorrhagic diathesis.

6) A wide range of laboratory parameters enables to state a more precise diagnosis of the hemostatic disorder and hemocoagulation, and thus to choose the appropriate therapy and at the same time also to check it up.

7) The examination of hemocoagulation indicators in patients with malignant tumour disease enables to reveal the risk of severe coagulation disorders and thus to choose the optimal preventive procedure.

8) Overall changes in hemostasis, coagulation and fibrinolysis can reflect the risk of thromboembolic complications, the fact of which reminds the necessity to apply the preventive therapy early enough. The development of hemostatic changes in neoplastic disease can be affected by various factors that can be influenced therapeutically. This therapy in turn improves the prospect of survival.

9) Early laboratory diagnosis can contribute to early disclosure of malignancy.

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