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LETTER TO THE EDITOR

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General Changes in Haemostasis in Gastric Cancer

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Local Changes in Haemostasis in Patients with Gastric Cancer

The authors Kovacova, E., Kinova, S. Duris, I. and Remkova, A. are presenting two clinical studies dealing with local and overall changes in haemostasis in gastric carcinoma. The subject described in both studies is extraceptional in national literature as well as world-wide. The authors' workplace and the authors themselves can prove and guarantee that both studies present new findings and surprising facts. The authors work at the clinic and are outstanding clinical researchers in the field of haematology, endocrinology and gastroenterology. They are also involved in the field of oncology. For example, Duris has been dealing with carcinogenesis, gastric precancerous conditions on the basis of histological, histoenzyme and cytological findings and with the relations between them and acid mucopolysaccharides in gastric juice for a decade. He has also been carrying out research in advanced gastric cancer and his effort has resulted into studies on this malignant prevention while applying non-steroid analgetics or calcium. Therefore it is no surprise that gastric carcinoma has become a model of examining haemostatic and haemocoagulation changes. Changes in haemostatic system are well-known in hematologic malignancies but in solid tumours are found on a relatively random basis. Most of them are examined in lungs carcinoma, colon, breast, kidneys, gall bladder, thyroid and pancreas. These changes and their description are not often found in gastric carcinoma.

This issue might not seem to be important in the gastric carcinoma examinations, as within late sixty years a marked reduction was observed in the incidence of gastric carcinoma, especially in women, in developed and developing countries. The incidence of gastric carcinoma in men decreased from 1349 to 511 in Slovakia in 1968–2003 and the reduction in the incidence of gastric carcinoma in women was from 902 to 334 within one year. The ratio of men to women equals 2:1, the ratio 1:1 is present only in the diffusion type. The incidence of gastric carcinoma represents 18.7/100,000 and the mortality rate is 14.6/100,000 in Slovakia. Not only the incidence rate but also the type of carcinoma has changed. Generally, the incidence rate of intestinal carcinoma that is usually diagnosed in elderly people and its genesis can be related to environmental factors, has declined. The incidence of diffused type of carcinoma, diagnosed more often in younger people and referred to genetic factors, has not been significantly reduced. Mainly following risk factors of gastric carcinoma are considered: smoking cigarettes, obesity, alcohol problem – large alcohol consumption, meat eating, and tooth loss. Infection with Helicobacter pylori has been linked with worsening the situation. Besides the incidence rate, the type and also localization of gastric carcinoma has changed. There are fewer carcinomas diagnosed in the gastric distal part and more disorders have been observed in the upper parts, cardia and lower part of the oesophagus and the histological composition has changed. More adenocarcinomas and less squamous cellular carcinomas have been observed and diagnosed in the above mentioned parts.

The reduction in the incidence of gastric carcinoma can be a result of introducing the process of cooling food instead of salting, smoking and marinating it. From this point of view there are a lot of studies describing the role of Helicobacter pylori eradication.

Although a lot of work has been done in this field, gastric carcinoma is still the most common cancer in the world and still preserves its outstanding position world-wide. The gastric cancer patients' prognosis has slightly changed towards a better prognosis, except for early gastric carcinoma. Although there is an increased number of endoscopic procedure, the detection of early gastric carcinoma has been still random. Thirteen per cent of men and sixteen per cent of women are likely to survive for five years in Slovakia.

From this point of view it can be concluded that authors of the studies have thoughtfully selected a solid organ, stomach, in which changes in haemostatic system are observed and investigated.

This issue links to some other disciplines and also specialists who are involved in the field of haematology, gastroenterology, oncology, cardiology, surgery, and intensive care. Internal medicine at the level of either pre-operation or post-operation assessment will find these studies interesting. They certainly will be interesting for an experimental oncology as the changes revealed and detected by the authors can cause and be the result of malignant lesions.

The study dealing with overall changes in haemostasis in patients with gastric cancer comprises a didactic division into studied changes in primary haemostasis (thrombocytes, thrombocytes aggregation, betathromboglobuline, thrombomoduline), studied plasma haemocoagulation system (prothrombin time, activated partial thromboplastin time, time of thrombine, fibrinogen and fibrin monomers). Next, there are inhibitors of blood coagulation (anti-thrombin III, protein C and S). The authors have linked euglobulin lysis, assessing and limiting plasminogene and fibrin degradation products to fibrinolytic system. Reading the paper one may think of various types of investigation that can be carried out and applied in a real patient with gastric carcinoma. Furthermore, the authors of the paper have achieved very interesting results. Very interesting is the fact that only 7.5 per cent of patients with gastric carcinoma had normal laboratory test results and findings that are mentioned above. Almost one third of patients have had hypercoagulation disorders and six per cent of patients have proved a developed syndrome of disseminated intravascular coagulation. Similar results have been obtained by those who studied similar changes in patients with carcinoma of other solid organs. Vein thrombosis and acute pulmonary embolism have been the most common diseases (22 %), while migrated superficial thrombophlebitis, septic thrombosis, acute disseminated intravascular coagulation and microangiopathic hemolytic anemia have been proved in approximately 7 per cent. It has been proved that anticoagulation and procoagulation changes have induced mainly prothrombotic condition. Eating habits and diet of patients with these disorders must be considered as well, as malnutrition patients have had significantly higher basal levels of alfa-1 acid glycoprotein, C-reactive protein and alfa-1 antitrypsin and lower level of transferrin and retinol-binding protein. Authors are trying to draw our attention to subclinical hypercoagulable conditions (this fact is another added value of this study) in accordance with other researchers/authors, especially Japanese ones, (Yamashita), who have focused on the importance of tissue factor (TF) as a prognostic indicator. Generally characterized, TF is best known as the primary cellular initiator of blood coagulation and allows vascular integrity. Another factor of prognosis can be the micro vessel density – MVD. It has been proved that a significantly higher level of TF and MVD is in correlation with the intestinal carcinoma but not a diffuse one. The main mechanism, as TF activates carcinoma progression, is a dependence on proteolytic activity of the complex extracellular TF and the factor VIIa. This complex generates thrombin and initiates its storing into microenvironment of the tumour thus activating the process of forming metastasis. It results in activation of histological deposits in the tumour stroma, especially in fibrinolytic activity disorders. As some papers proved, fibrin deposits in tumour stroma are derived from plasmatic fibrin, fibrin plays an important role in forming metastasis. Another important effect of the TF is an increased VEGF production. VEGF is employed in angiogenesis.

Authors of these papers have discussed and pointed at the higher levels of fibrinogen, the importance of angiogenesis in treating gastric carcinoma. Increased TF and MVD levels have been reported in colorectal carcinoma, prostate, pulmonary and liver carcinoma. It is interesting that in the case of gastric carcinoma, TF and MVD increased levels are of importance only in case of intestinal type of carcinoma and not a diffuse one.

The other study is aimed at local haemostatic changes in gastric carcinoma. The authors have studied procoagulation and fibrinolytic activity of gastric juice to assess plasma recalcification time, alpha-1 glycoprotein, alpha-1 antitrypsin, and fibrinogen and D-dimer levels.

Another very positive fact is that this study is dealing with changes in pre-cancerous conditions. A partial drawback is that the authors are not describing the way of extracting the gastric juice, whether juice is extracted in a classical extraction via a gastric tube or throughout endoscopy. One has to admit that the number of positive Helicobacter pylori patients in all groups – malignant, precancerous and control groups – is not clear.

The positive fact is that new results have been gained in the field of coagulation activation, inhibition of the fibrinolytic system and fibrin degradation products in gastric juice. This can possibly explain and reason different diagnoses for massive bleeding from ulcers and occult bleeding in gastric carcinoma.

Pepsin activity influencing clot formation depended on acidity must be taken into consideration, for example thrombocytes function is in an extreme disorder when the pH level in vitro is low. Thus acidity reduction to a neutral level can cause coagulation stabilisation, can modify thrombocytes function and can influence bleeding prevention.

Both studies have presented excellent results with a high priority gained in the process of examining a considerably large number of patients with gastric carcinoma. The study on overall changes in haemostasis comprises 67 patients with gastric carcinoma and in the study on local changes in haemostasis there were 33 patients with gastric carcinoma and 31 patients with precancerous conditions. The control groups are alligned with the above mentioned groups.

Personally as a practising gastroenterologist and mainly clinical doctor involved in internal medicine, I consider these studies very thoughtful as they are aimed at the conditions of subclinical thrombofilia, especially in the risks of severe complications based on haemostasis disorders that are often underestimated in practice.

Valuable contributions of both studies are recommendations how to improve the patients' survival presented by authors. According to the results described in the studies, haemostatic changes that are actively influenced can prevent the progress of disease although the disorder is reduced through a surgery, radiation, cytostatic, endoscopic or palliative treatment.

Gastroduodenal stent can be given as an example. The stent is used in advanced malignancies where this type of treatment is contraindicated due to coagulopathy and enteral ischemic disorder, etc. Patients with the above mentioned disorders can benefit when haemostatic changes are influenced in a right way.

At the end we must emphasize the authors' conclusions that haemostatic changes with no symptoms and revealed by chance can be considered as a marker of a possible malignancy, especially because in our practice we often prefer to examine and assess different types of tumour markers.

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