

## PROCOAGULANT ACTIVITIES IN THE PLASMA OF A PATIENT WITH PERITONEAL METASTASIS FROM PANCREATIC NEUROENDOCRINE TUMOR: A CASE REPORT

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## ПРОКОАГУЛЯНТНАЯ АКТИВНОСТЬ ПЛАЗМЫ КРОВИ У ПАЦИЕНТА С НЕЙРОЭНДОКРИННОЙ ОПУХОЛЬЮ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ И ПЕРИТОНЕАЛЬНЫМИ МЕТАСТАЗАМИ

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We report a case of peritoneal metastasis from pancreatic neuroendocrine cancer occurring in a 58-year-old male. The disease showed a profound perturbation of haemostasis with a 15-fold increase in prothrombin activation fragment 1+2 ( $F_{1+2}$ ), a marker of thrombin generation, combined with high levels of fibrinogen and d-dimer. This testifies the high thrombotic risk in patients with advanced pancreatic cancer of neuroendocrine origin and prophylactic use of low molecular weight heparin might be warranted in order to decrease the incidence of thrombotic events and thromboembolic complications in these patients.

**Key Words:** peritoneal metastasis, pancreatic cancer, deep venous thromboembolism, low molecular weight heparin, d-dimer, prothrombin 1+2 fragment.

Сообщается о случае перитонеального метастазирования нейроэндокринной опухоли поджелудочной железы у 58-летнего пациента. Заболевание проявлялось в выраженном нарушении гемостаза, 15-кратном повышении уровней фрагмента 1+2 ( $F_{1+2}$ ) протромбина, маркера образования тромбина; фибриногена и d-димера. Эти данные свидетельствуют о высоком риске тромбообразования у пациентов с развитым раком поджелудочной железы нейроэндокринного генеза. Для снижения риска тромбообразования и развития тромбоэмболических осложнений у таких пациентов оправданным является профилактическое применение низкомолекулярного гепарина.

**Ключевые слова:** перитонеальные метастазы, рак поджелудочной железы, глубокий тромбоэмболизм сосудов, низкомолекулярный гепарин, d-димер, фрагмент 1+2 протромбина.

Deep venous thromboembolism (DVT) is a common complication in cancer patients [1]. Its incidence is ranging from 1 to 60% [1, 2]. In particular, pancreatic malignancies are associated with an increased risk of venous and arterial thrombosis [3, 4] as well as of disseminated intravascular coagulation (DIC) [5, 6]. However, the mechanism underlying the increased susceptibility to DVT in malignancies is not fully understood [7–9], in particular in pancreatic cancer [3, 10, 11].

We report a case of peritoneal metastasis from pancreatic neuroendocrine cancer showing a profound perturbation of haemostasis. DVT, in fact, is an important factor for morbidity and mortality of cancer patients [3] and the 15-fold increase in prothrombin activation fragment 1+2 ( $F_{1+2}$ ), a marker of thrombin generation, combined with high plasma levels of fibrinogen and d-dimer reported in the case confirm the risk of thrombotic event in these patients.

**Case report.** A 58-year-old male was admitted to our Institute with ascites. Physical examination showed hepatomegaly and splenomegaly. Laboratory findings for hepatitis B and C virus did not reveal any infection so excluding chronic liver disease; erythrocytation rate (ESR) at first hour was 56 mm, red blood cells 3.800.000/ $\mu$ L, hemoglobin 10.9 g/dl, red cellular medium volume 81 fL, medium cellular hemoglobin 28 pg, white blood cells 6.700/ $\mu$ L, platelets 118.000/ $\mu$ L.

Oncological markers revealed an increase in gastrointestinal cancer antigen (GICA: 93 U/mL), carcinoembryonal antigen (CEA: 73 U/mL). Moreover, ultra-

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**Abbreviations used:** APCr — activated protein C resistance; aPTT — activated partial thromboplastin time; AT III — anti-thrombin III; CEA — carcinoembryonal antigen; DIC — disseminated intravascular coagulation; DVT — deep venous thromboembolism; ESR — erythrocytation rate;  $F_{1+2}$  — prothrombin 1+2 fragment; GICA — gastrointestinal cancer antigen; PAI-1 — plasminogen activator inhibitor type 1; PT — prothrombin time; t-PA — tissue plasminogen activator.

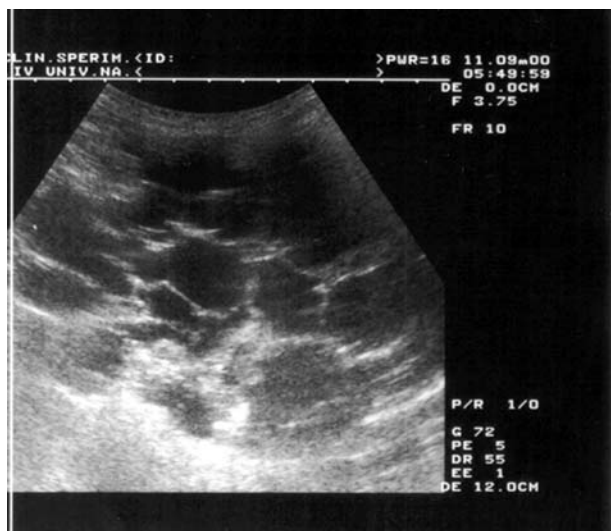
sonographic examination showed septated ascites of neoplastic nature due to peritoneal metastasis (Figure). The subsequent abdominal TC examination confirmed the presence of peritoneal metastasis from pancreatic tumor with multiple swelling of retroperitoneal, retro-pancreatic, periaortic, perihepatic lymph nodes. Finally, cytology on ascitic fluid showed presence of malignant cells of neuroendocrine origin and the chemotherapy was started.

In order to evaluate the alteration of haemostasis of the oncological patient we determined prothrombin time (PT as International Normalized Ratio, INR), activated partial thromboplastin time (aPTT as ratio), fibrinogen, C protein, S protein, antithrombin III (AT III), activated protein C resistance (APCr, according with the method described by Dalback), prothrombin 1+2 fragment ( $F_{1+2}$ ), d-dimer (a marker of stabilized fibrin degradation), tissue plasminogen activator (t-PA), plasminogen activator inhibitor type 1 (PAI-1). However, haemostasis laboratory tests are summarized in Table.

**Table.** Clotting parameters in a patient with peritoneal metastasis from neuroendocrine pancreatic cancer

Test	Normal value	Case data
PT (INR)	0.8–1.2	1.12
aPTT (RATIO)	0.8–1.2	1.09
Fibrinogen (mg/dl)	200–400	488
Protein C (%)	60–130	88
Protein S (%)	78–130	93
AT III (%)	80–120	72
APCr (Dalback method)	> 0.77	0.94
$F_{1+2}$ (nM)	0.4–1.1	16.23
d-dimer (ng/dl)	<0.05	5.88
t-PA (ng/dl)	1.5–12	8.7
PAI-1 (ng/ml)	4–45	81

Laboratory findings demonstrated a hypercoagulable state associated to a reduction of fibrinolysis. The hypercoagulable state was testified by a strong increase in thrombin generation ( $F_{1+2}$  plasma levels 16.23 nM, normal values until 1.1 nM), increased plasma fibrinogen levels (488 mg/dl), increased d-dimer plasma rate (5.88 ng/dl) and reduction of AT III plasma concentration (72%), while normal plasma concentration of t-PA (8.7 ng/dl) and increase in PAI-1 concentration (81 ng/ml)



**Figure.** Ultrasonographic image of septated ascites of neoplastic nature due to peritoneal metastasis

confirmed the alteration of fibrinolysis. Normal values for PT, aPTT, C protein, S protein were also discovered. Because the combined increase in thrombin generation, d-dimer and fibrinogen plasma levels associated to reduction of fibrinolysis represent a risk for thrombotic events, a treatment with low molecular weight heparin (LMWH), reviparin 4200 UI daily was started.

Thrombosis is a frequent event in cancer patients [1–3]. A thrombophilic state is present during natural history of cancer related disease [8]. Venous thromboembolism, in fact, may be revealed in about 1–60% of cancer patients [1–3]. Thrombosis may occur as an early or a late sign during oncological disease, but in advanced stage thrombosis is the most common complication of oncological disease [3, 8]. The mechanism whereby cancer induces activation of haemostasis is still not completely understood but many pathways are involved [8, 12].

In particular, pancreatic malignancies are often complicated by thrombotic events including DVT, arterial thrombosis and DIC [3–6]. We studied haemostasis in a patient admitted to our Division because of advanced pancreatic neuroendocrine tumor complicated by peritoneal metastasis. A 15-fold increase in plasminic prothrombin activation fragment 1+2 was found thus indicating a strong increase in thrombin generation. Moreover, AT III reduced plasma level suggested AT III consumption to counteract increased thrombin generation. We also found an increase in d-dimer and fibrinogen plasma concentration, as markers of hypercoagulable state. Furthermore, we reported also alterations in fibrinolytic pathway with a trend toward hypofibrinolysis testified by normal values in t-PA levels associated with strong increase in PAI-1 levels. Altogether, this data suggest an increased risk for thrombotic events and a treatment based on LMWH was needed to reduce the risk of following thrombotic events.

Yet, the mechanism underlying the increased thrombotic risk in pancreatic cancer is not fully understood. However, an altered protease/antiprotease balance is involved as an altered clotting/anticoagulation balance [8, 13]. The expression of these alterations with a trend toward thrombophilia is testified by increased production or a decrease in inhibition of prothrombinase (i.e. clotting factor Xa) in cancer patients [14]. An elevated Xa production could be related, in fact, to the increased release of cancer procoagulant by cancer cells [15] and/or localization of factor X in pancreatic tissue [11], while a decrease in Xa inhibition might be partially contributed to by a reduction in heparan sulphate due to an increased production of heparanase by cancer cells [14, 16–18]. Prothrombinase (i.e. clotting factor Xa), in fact, cleaves prothrombin (clotting factor II) synthesized by liver as a zymogen, producing  $F_{1+2}$  and thrombin [19]. Moreover, peculiarity of the case described is related to the strong increase in thrombin generation combined to the increased release of fibrinolysis inhibitor (i.e. PAI-1). Hypofibrinolysis, in fact, could be related to the peritoneal involvement. Physiologically in fact peritoneum shows a strong fibrinolytic activity [20].

In conclusion, our study suggests that in a patient with advanced pancreatic cancer of neuroendocrine origin, there is an increased thrombotic risk due to the increased thrombin generation and alterations of fibrinolysis. Prophylactic use of low molecular weight heparin might be warranted in order to decrease the likelihood of thrombotic events in these patients, because of their selected inhibition of prothrombinase, in order to reduce morbidity and mortality of oncological patients related to thromboembolic complications.

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