Increased D-dimer value and occult cancer in the absence of detectable thrombosis

Fibrin formation and removal occurs continuously during the development of malignancy. Accordingly, hemostatic disorders in cancer patients are a rather frequent observation and range from asymptomatic laboratory changes to massive thromboembolism or haemorrhage. We document the case of an asymptomatic women, who was enrolled as a healthy control in a study and showed up with a substantially increased D-dimer value. After ruling out the most probable sources of D-dimer elevation, such as thrombosis, inflammation and trauma, she underwent laboratory and radiological investigations for malignancy, which were consistent with a colorectal metastatic adenocarcinoma. This case allow us to hypothesize that screening for occult malignancy in the presence of apparently inexplicable elevated D-dimer values may be taken into consideration

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Case report. A 46 years old women voluntarily participated as a healthy control in a study for the evaluation of a new D-dimer assay. The value of her D-dimer was substantially elevated (2554 ng/mL) and outside the actual reference range for this assay (<500 ng/mL). Although in a healthy status and apparently asymptomatic, she was referred to our local emergency department, where she underwent an accurate physical examination, appropriate laboratory testing and ultrasonography of the lower limbs. The familiar and personal clinical history were both negative for thromboembolic events and the ultrasound of the lower limbs did not reveal visible thrombosis, either remote or actual. The patient did not refer any clinically significant symptom occurred over the last year, besides minor and occasional rectal bleedings, attributed to the presence of grade IV haemorrhoids. Besides the confirmed D-dimer increase, most results of laboratory testing were within the respective reference ranges (Table 1). Since the outcome of the clinical investigation and laboratory testing were not suggestive for any additional source of D-dimer elevation, an extensive tumor markers screening was planned, which revealed a remarkable elevation of CA 19-9 (34356 U/mL, reference range: <25 U/mL), and modest elevation of CEA (30 ng/mL, reference range: <5 ng/mL), whereas results of CA 125, CA 15-3, tyreoglobulin and NSE were within the respective reference ranges. The patient was referred to the radiology department for abdominal ultrasound examination, which revealed diffuse liver metastases and a suspect metastatic abdominal lymph. The total body computerized axial tomography, which was suddenly performed, showed a 6x4 cm primary mass located in the caecum and diffusely infiltrating the perivisceral fat, diffuse metastatic liver involvement (8 to 12 metastases, with a major diameter of 4 cm), a large metastatic abdominal lymph (diameter of 5 cm) and a single metastatic involvement of the right lung (diameter of 0.62 cm). The results of colonoscopy and histological examination of biopsies confirmed the original diagnostic suspect of a primary adenocarcinoma of the caecum. The patient is currently undergoing chemotherapy.

Discussion. There is a well-known interaction between haemostasis and cancer, which holds considerable promise for gaining new understanding of tumor biology.[1] Venous thromboembolism (VTE), and particularly idiopathic VTE, occur with a prevalence that approximates 10% as a paraneoplastic phenomenon, which was firstly described by Trousseau in 1865 (Trousseau syndrome).[2] Patients with malignancy, in particular those with solid tumors, are characterized by a net haemostatic imbalance and the tumour itself is the origin of hypercoagulability.[3] In the specific case of colorectal cancer, the postoperative risk of thromboembolic events was reported as approximately 2% to 5%.[4] Development of cancer is therefore associated with activation of blood coagulation and results of laboratory tests clearly demonstrate that fibrin formation and dissolution is continuously ongoing at different rates.[5] Notably, fibrin formation is also involved in the process of tumor spread and metastasis. Accordingly, the mean global fibrinolytic capacity, appears substantially increased in patients with colorectal cancer either before and after surgery.[4]

Substantially elevated and apparently inexplicable plasma D-dimer values at presentation are markers of poor overall survival, event-free survival and underlying malignancy. The most frequent abnormalities of routine clotting tests in cancer patients are increased levels of fibrinogen, factor (F)V, FVIII, FIX, FX, fibrin(ogen) degradation products (FDPs), and thrombocytosis.[6] The preoperative concentration of several prothrombotic markers, especially D-dimer, is associated with relatively advanced tumor stage and short postoperative survival after curative resection.[7,8] Additional clinical investigations demonstrate that the measurement of preoperative D-dimer level would be useful in the preoperative staging, lymph node metastasis and prediction of postoperative survival in patients with colorectal cancer.[9-11] Therefore, screening for this malignancy in the presence of apparently inexplicable elevated D-dimer and advanced age may be taken into consideration.[8,12,13] The usefulness of this approach has been highlighted in a clinical investigation on patients with deep vein throm-

Table 1. Results of laboratory testing and relative reference ranges

	Test result	*Reference range*
Prothrombin time (INR)	1.09	0.83-1.11
Activated partial thromboplastin time (ratio)	1.10	0.85-1.17
Fibrinogen (mg/dL)	374	150-400
D-dimer (ng/mL)	2557	<500
Hemoglobin (g/dL)	12.0	12.0-16.0
Hematocrit	0.35	0.35-0.45
Red blood cell count (x12/L)	4.27	3.80-5.10
White blood cell count (x12/L)	9.88	4.30-10.0
Platelets (x12/L)	395	150-400
Alanine aminotransferase (IU/L)	28	6-40
Lipase (IU/L)	30	13-60
Pancreatic amylase (IU/L)	37	28-100
Total bilirubin (mg/dL)	0.40	0.20-1.10
Creatinine (mg/dL)	0.64	0.50-1.20
Urea nitrogen (mg/dL)	8.6	8.0-22.0
Glucose (mg/dL)	106	60-110
Albumin (g/L)	38	32-50
Erythrosedimentation Rate	22	<38

bosis recently appeared in this Journal, which demonstrated that high D-dimer concentrations at presentation or during the first days of treatment are indicators of an increased probability of overt or occult forms of cancer, especially in patients under 60 years old.[14] In particular, 23% of patients with thrombosis were diagnosed as having a malignancy in the study period. High initial D-dimer levels (levels >4000 mg/L) were also associated with more cancer during the 34 months of follow-up than were lower D-dimer levels. Finally, high D-dimer levels after 4 days of treatment were associated with a three-times greater prevalence of cancer.[14] The search for activation of hemostasis is also important in patients without known cancer, to identify those more prone to develop thrombosis. The laboratory approach include elevation of clotting factors, such as fibrinogen/fibrin degradation products, hyperfibrinogenemia and thrombocytosis and elevation of specific markers of activation of coagulation, such as fibrinopeptide A, fragment 1 + 2, thrombin-antithrombin complexes and D-dimers.[15]

Regardless of these clinical evidences, no clinical study has yet been published on the relationship between pathological D-dimer values and occult cancer in the absence of detectable thrombosis to the best of our knowledge. Accordingly, there is no warning on the potential convenience of screening for occult cancers in patients presenting with substantially elevated D-dimer, once thrombosis and other physio-pathological sources of elevation (trauma, pregnancy, liver or renal failure, inflammation) have been excluded by clinical assessment, laboratory and radiological investigations. The only clinically meaningful symptom reported by this patient was an occasional rectal bleeding, which was attributed to the presence of grade IV haemorrhoids. The great majority of adults referred with this symptom have a very low risk of serious diseases such as cancer or ulcerative colitis, but a high chance of haemorrhoids or anal fissures. Accordingly, it has been estimated that 50% of the population has haemorrhoids by the age of 50.[16] A large variety of closely related conditions, such as colon cancer, may be classified as haemorrhoids, as the clinical symptoms can mask or mimic more important and serious diseases, leading to misdiagnosis or delayed identification of cancer.

Conclusions. There is a well established association between idiopathic VTE and occult cancer. Although the development of VTE in a patient with known cancer is a very frequent presentation, in some patients it may precede the diagnosis of malignancy by many months. The variation in clinical presentation is probably due to the heterogeneous biology of different tumor types and also reflects the limitations of detection or available diagnostic methods.[17] High D-dimer concentrations at presentation in patients with VTE or during the first days of treatment are therefore indicators of an increased probability of overt or occult forms of cancer,[14] that can be detected by extensive diagnostic investigation.[17] Although we can not conclude that D-dimer concentration can be always used as a predictor of cancer, the otherwise inexplicable increase observed in this case can be interpreted as the most likely epiphenomenon of an occult adenocarcinoma of the caecum. This is consistent with the evidence that patients with colorectal cancer, especially those with metastatic disease, are characterized by hypercoagulability and increased global fibrinolytic capacity.[3-4,19-20]

The value of screening patients with idiopathic VTE or increased D-dimer for occult cancer is still under debate, and randomized studies are required to establish its potential cost-effectiveness.

Although screening for occult cancer in patients with unexplained high D-dimer is not supported by studies on its efficacy on the overall mortality, this diagnostic suspect may offer possible chances for anticipated diagnosis in specific patients with a very high D-dimer level which can not be explained otherwise and who have clues in their medical history suggesting possible malignancy.

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