THE “DARK SIDE” OF DEEP VEIN THROMBOSIS - CASE REPORT

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THE “DARK SIDE” OF DEEP VEIN THROMBOSIS - CASE REPORT (Abstract): Venous thromboembolism (VTE) is an increasingly common cause of morbidity and mortality in cancer patients. In various malignancies the incidence of thrombosis ranges from 5% to 60%, that is four times higher in cancer patients compared to the general population. Large retrospective studies have shown that in men the tumors which are most commonly associated with VTE are lung cancer and pancreatic cancer and, in women cancer of the genital area, pancreas, colon and rectum. Thromboembolic events may often occur before the cancer diagnosis. We present the case of a 41-year-old female patient with a history of genital cancer which was surgically treated and who is now admitted for clinical signs of ileofemoral deep vein thrombosis (DVT) of the left leg. The diagnosis was confirmed by laboratory data and Doppler ultrasound and the patient received anticoagulant treatment. Given the history of the patient, abdominal and pelvic ultrasound and computer tomography (CT) were performed to detect the cause who predisposed to the thrombotic event. These confirmed the ovarian cancer, this time on the right side, and the presence of hepatic and pulmonary metastasis. This case highlights the importance of screening for a cause of the thromboembolic event in patients, especially in those who have a history of a neoplasia. Keywords: DEEP VEIN THROMBOSIS, MALIGNANCY, PARANEOPlastic SYNDROMES.

The association between malignancy and clinically manifest thrombosis in various sites has been recognized for almost 140 years. It was first described by Armand Trousseau in 1865 who noted that “in cancer patients a special condition of the blood predisposes to spontaneous coagulation” (1, 2). Hypercoagulable state is a characteristic of cancer patients and the spectrum of hemostatic disorders extends from abnormal coagulation tests in the absence of clinical signs, to massive thromboembolism at various sites (2 - 4). Thrombotic episodes may precede malignancy by months or days and can manifest in various forms: superficial migratory thrombophlebitis (Trousseau syndrome), nonbacterial thrombotic endocarditis, disseminated intravascular coagulation – DIC (malignancy is considered the third cause of DIC after infection and trauma), thrombotic microangiopathy. Arterial thrombosis can also occur (but less frequently than vein thrombosis), and is due to nonbacterial thrombotic endocarditis (2). The incidence of thrombosis ranges from 5% to 60% in vari-
ous malignancies, which is four times higher in cancer patients compared to the general population (3). In men, pancreatic and lung cancer are most commonly associated with VTE and in women - the genital area, pancreatic and colorectal cancer (5). It is worth remembering that not infrequently vein thrombosis may precede by a variable period of time the occurrence of the specific clinical picture of cancer (2).

CASE REPORT

We present the case of 41-year-old woman who was admitted to the Department of Cardiology, „Sf. Spiridon” Emergency Clinical Hospital Iași, for edema and pain in the left leg, occurring relatively quickly, in the last 48 hours, suggestive for the clinical diagnosis of iliofemoral thrombosis of the left leg.

The past medical history revealed that at the age of 37 years she underwent left oophorectomy and subtotal hysterectomy for ovarian tumor, the anatomopathological diagnosis findings being low-grade malignant stromal sarcoma, for which chemotherapy was not indicated but periodic check-ups were recommended. The current diagnosis of deep vein thrombosis was confirmed by the presence of elevated raised D-dimers and Doppler ultrasound of the lower legs which showed incomplete thrombosis of the left external iliac, left common femoral and left popliteal veins (fig. 1).

Laboratory data revealed: a mild inflammatory syndrome (ESR: 57 mm/h, fibrinogen: 5.65 g%), normal white blood cell and platelet counts, absence of anemia, negative result in antiphospholipid antibody test (the latter excluding a possible thrombophilia). The remaining laboratory data were within normal range.

Unfractionated heparin therapy via syringe pump monitored with activated partial thromboplastin time (APTT) was initiated, and laboratory tests were performed to elucidate the cause of DVT (fig. 2).

Given the history of genital cancer, abdominal and pelvic ultrasound scan was performed, which showed a cystic mass on the right ovary associated with liver metastases. Chest X-ray demonstrated pulmonary metastases, all these changes being confirmed by thoracoabdominal CT which in
its turn confirmed that the right ovarian cystic mass detected by ultrasound was in fact a right ovarian cystic neoplasm with liver and pulmonary metastases.

The final diagnosis was: paraneoplastic left iliofemoral vein thrombosis, right ovarian cystic cancer, liver and lung metastases.

**Fig. 2.** A: Chest X-Ray showing left pulmonary metastases; B: Abdominal ultrasound showing liver metastases; C: Abdominal CT showing liver metastases; D: Pelvis ultrasound scan showing ovarian cysts with signs of malignancy

**DISCUSSION**

The occurrence of a prothrombotic status in cancer patients depends on the type, location and extent of the tumor, response of the host organism, as well as on therapeutic regimens used (2, 6, 7). The main mechanisms involved in the induction of prothrombotic states are:

- excessive thrombin production by an extrinsic pathway due to secretion by certain tumors of tissue-like factors (e.g.: gastric and pancreatic tumors) (2, 8, 9); these tumors frequently cause recurrent and migratory venous thrombosis (Trousseau) (2);

- production of thrombin directly by intact tumor cells that may express procoagulant activity; sometimes normal host tissues can express procoagulant activity in response to the tumor.

Malignant tumors can secrete substances with procoagulant activity mainly of two
types: tissue factor and cancer procoagulant. Tissue factor forms a complex with activated factor VII and factor IX and X leading to the initiation of coagulation and cancer procoagulant is a calcium-dependent cysteine protease which directly activates factor X, independent of tissue factor and activated factor VII (2). Monocytes, which normally do not have procoagulant activity can be stimulated, under certain conditions, to produce tissue factor or other direct activators of factor X by T lymphocytes, antigens, cytokines, lipoproteins, immune complexes, endotoxins (2). Also, the presence of a malignancy in the body produces an abnormal platelet activation which aggravates the hypercoagulable state. The endothelial cells may become procoagulant under the influence of pro-inflammatory cytokines or other peptides, and in particular due to TNF and IL-1 which increase the expression of leukocyte adhesion molecules, platelet activating factor and tissue factor. TNF also reduces the fibrinolytic activity of endothelial cells, increases endothelial production of IL-1 and expression of thrombomodulin which decreases the anticoagulant protein C activation (2, 8 - 10). Additional risk factors for VTE in patients with malignancies include: age, race, comorbidities, history of VTE, cancer site, metastases, recent surgeries, chemotherapy, central venous catheters and sepsis (2, 8 - 11). The period of 3-6 months after diagnosis is characterized by an increased incidence of VTE. Another mechanism by which malignant tumors can cause venous thrombosis, besides inducing hypercoagulable state, is extrinsic compression or direct vascular invasion (2, 11).

The literature review showed that different reported cases of VTE episodes were in the end diagnosed with occult malignancy (12 - 19). Each of them has its particularities: atypical location of venous thrombosis, bilateral involvement, or different types of cancer. As to the tumor markers, which were negative in our patient, cases reported in the literature presented either positive or negative tumor markers, depending on the histopathological type (13, 14, 20).

**CONCLUSIONS**

There are some particularities of this case: 1) Discovery of a cancer relapse in metastatic stage in the guise of DVT; 2) Paraneoplastic DVT usually occurs in adenocarcinomas (in our case the first tumor was low-grade malignant stromal sarcoma); 3) Absence of tumor markers even in the presence of metastases.

We believe that clinical history taking, routine laboratory findings, together with chest X-Ray and abdominal ultrasound are valuable screening tools for occult malignancy, especially in cases with atypical form or apparently idiopathic VTE.

**REFERENCES**

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