ASPECTS OF VASCULAR ULTRASOUND IN DEEP VENOUS THROMBOSIS ASSOCIATED WITH MALIGNANCY

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SUMMARY:
Deep vein thrombosis is a major venous pathology and also severe because of its complications: pulmonary embolism and postthrombotic syndrome. Patients with cancer are at high risk of deep vein thrombosis of lower limbs presenting since they have a cluster of risk factors. Venous ultrasound, by compression and Doppler techniques, with a very high sensitivity and specificity for femoral-popliteal deep vein thrombosis represents the ideal non-invasive diagnosis method. The study aims to identify some ultrasound issues in patients with cancer and associated thrombosis: positive diagnosis, localization, extension of thrombosis, correlation with symptoms, progressive features.

Keywords: deep vein thrombosis, cancer, vascular ultrasound.

Rezumat: Tromboza venoasă profundă reprezintă o patologie venoasă importantă prin complicațiile pe care le poate determina, respectiv embolia pulmonară sau sindromul postthrombotic. Pacienții neoplazici prezintă un risc crescut de tromboză profundă a membrelor inferioare prezentând un cumul de factori de risc. Ultrasonografia venoasă, prin tehnici de compresiune și Doppler, având o sensibilitate și o specificitate foarte ridicate pentru tromboză venoasă profundă femuro-popliteală reprezintă metoda ideală de diagnostic non-inaviz. Studiul și-a propus identificarea unor aspecte ecografice la pacienți cu neoplazii și tromboză venoasă profundă asociată: diagnostic pozitiv, localizarea, extinderea trombozii, corelația cu simptomatologia, particularități evoluтиве.

Cuvinte cheie: tromboză venoasă profundă, neoplasm, ultrasonografie vasculară

INTRODUCTION
Deep vein thrombosis is the main cause of pulmonary embolism. Diagnosis is usually based on history, physical examination, ultrasound and dosage D-dimers. Establishing early diagnosis is of particular importance because thrombus can be extended, and the disease can be fatal by producing pulmonary embolism or disabling by developing postthrombotic syndrome. Cancers, especially those in the pelvis are often accompanied by deep vein thrombosis, which is sometimes the first sign of the existence of cancer, and can represent the moment of the positive diagnosis. Vascular ultrasound is an effective, non-invasive, reproducible, extremely useful in the diagnostic of DVT and later complications (chronic venous insufficiency and postthrombotic syndrome). The role of vascular ultrasound is particularly important for cancer patients who have consistently elevated D-dimers even in the absence of DVT.

MATERIALS AND METHODS
We studied a group of 91 patients with deep vein thrombosis with or without pulmonary embolism, admitted to the Cardiology Clinic of the Emergency County Hospital Timisoara, of which 54 were women and 37 men with a mean age of 52± 16.7 years, range between 21-86 years, median 63. Age distribution was as follows: 5 patients between 20-29 years, 6 patients

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between 30-39 years, eight aged 40-49 years, 19 patients 50-59 years, 21 patients between 60-69 years 2021 patients between 70-79 years and 11 between 80-89 years. In terms of demographic distribution of study group, 59 (65%) patients were from urban areas and 33 (36%) from rural areas.

Were excluded patients who had had other causes of unilateral leg edema (lymphatic, rheumatic or inflammatory causes - cellulitis, erysipelas, arthritis, traumatic edema, etc.) or bilateral (primary chronic venous insufficiency, abnormalities of the inferior vena cava, heart failure, etc.); there were included only patients who have had imagistic documented the existence of venous thrombosis.

We noted thrombogenic risk factors: recent surgery, stroke, puerperium, pelvic or lower limbs fractures, previous cancer diagnosis. To confirm DVT venous ultrasound was performed using ALOKA SSD-4000 machine with 7.5 to 10 MHz linear array. During the initial examination the patient was supine with the hip in slight abduction and external rotation; in this position there were examined bilaterally symmetrical: common femoral vein, superficial femoral vein, profound femoral veins and great saphenous veins. Examination of the popliteal space and calf was performed with the patient in lateral, ventral decubitus or sitting position. Doppler examination methodology included the static examination with recording the spontaneous flow and the presence of respiratory modulation and also dynamic examination with provocative maneuver, such as venous compression with the transducer, upstream muscle compression, passive or active lifting leg, foot finger movement, abdominal compression and Valsalva maneuver. Vascular ultrasound was performed in patients with suggestive symptoms of DVT and in patients diagnosed with pulmonary embolism.

Positive diagnosis was made after ultrasound evaluating in the B mode, pulsed Doppler, Color and Power. During the examination were evaluated both direct, indirect signs and minor and major signs of deep vein thrombosis. (1,3). Suggestive imaging signs of thrombosis in two-dimensional ultrasound mode are:

- Major signs: direct visualization of thrombus in the lumen and vein incompressibility
- Minor signs: venous distention, fixed venous valves, lack of venous dilatation during proximal compression or Valsalva maneuver, increased spontaneous echogenicity of the blood flow.

Diagnosis of thrombosis by pulsed Doppler is determined by the following signs: absence of Doppler signal (direct sign) and reduction of spontaneous or provoked amplitude attenuation response to dynamic tests, no respiratory modulation, absence of normal venous flow behavior in Valsalva maneuver, no compressive distal flow augmentation at lifting the leg,
speeding the flow in the collateral branches of the great saphenous vein and large developing collateral circulation, increase blood flow velocity in stenosed segment (indirect signs).

Signs of acute thrombosis and information provided by Doppler examination are: absence of color in the vein spontaneously or after application of provocative maneuvers in case of complete obstruction, visualization of the thrombus (“gap flow”) in case of incomplete obstruction, delimits the end top of the thrombus, shows the peripheral residual lumen in acute thrombosis and central residual lumen in chronic thrombosis, identifying of venous topography and the collateral circulation, facilitates global venous exploration.

Examination of patients was made in the first two days of admission, within 0-7 days after onset of symptoms.

RESULTS

Of all enrolled patients, 34 presented various malignancies (previously documented or diagnosed during hospitalization for DVT): cancer of the uterus, ovary, kidney, prostate, bladder, colon, vagina, pancreas, brain, blood malignancy. Of these 28 (82%) were women and 6 (18%) men. Regarding the location of the tumors, pelvic ones were found to have been the majority (67%); the contributing factors were represented by neighborhood, with direct local expansion, the secretion of specific solid tumors thrombogenic factors and favoring stasis by compression on large vessels (iliac veins, inferior vena cava).

Distribution by age of deep venous thrombosis in neoplastic patients showed an proportional increasing by age between 40 and 80 years and a lower prevalence over 80 years; in this group were included fewer patients.

45% of patients were from rural areas and 55% in urban areas.

Another risk factor in the occurrence of DVT in cancer patients is curative or palliative surgery who was found in 19 (56%) of patients.

Concerning the localization of venous segment in DVT cancer patients we found that common femoral vein was affected in 25 (73%) of cases, superficial femoral vein in 17 (50%), deep femoral vein in 3 (9%), popliteal vein in 6 (18%) and calf veins in 6 (18%) of patients. 27 (79%) of cancer patients had unilateral and 7 (21%) had bilateral venous thrombosis. In terms of location of symptoms 24 (70%) patients experienced calf edema, 6 (18%) associated thigh and calf edema, and 2 (6%) phlegmatia coerulea dolens; 2 (6%) were patients with pulmonary embolism, without showing clinical signs of DVT. Particularly, in patients with peripheral subtle symptoms, ultrasound found that deep veinang2057 thrombosis was extended to the femoral vein too (56%); also we have documented impaired common iliac vein in 5 (15%) of patients. 12 (35%) of patients in the study were diagnosed with cancer during in hospitalization for deep vein thrombosis. 22 (65%) of patients were
reviewed imaging at 3 months after admission. At the 32 (94%) survivors were noted reducing vascular venous thrombosis and number of venous segments affected in only 10 (pard 1 (31%) of patients; in contrast to the remaining 22 (69%) patients were not found significant ultrasound changes, despite symptoms improvements (pain and reducing the swelling).

**CLINICAL CASE 1**

Patient S.L. 62 years old, with known genital tumor, is addressed to the Cardiology Clinic of County Emergency Hospital Timisoara presenting pain and edema of the entire right leg. On physical examination there was noted hepatomegaly with hard consistency and irregular surface, unilateral edema in the right calf and thigh, positive Homans sign.

Abdominal ultrasound images showed inhomogeneous hypoechoic images with hyperchoic contour, oval, with an average diameter of about 2 cm, in the caudate and the left hepatic lobe, suggesting secondary determinations in liver.

Venous vascular ultrasound in the ilio-femoral-popliteal axis noted no Doppler signal in the common iliac vein, dilation of superficial femoral vein (with diameter of 12.4 mm), showing a hyperechoic homogeneous image suggesting a recent thrombosis, with extending to the profound femoral vein and the sapheno-femoral junction.

The treatment with unfractionated heparin by continuous infusion, with doses adjusted according to aPTT, conducted to clinical improvement, ie pain relief and significant reduction of edema.

The case is a common type of DVT associated neoplasia in a patient with uterine cancer and liver metastases.

**CLINICAL CASE 2**

Patient B.V. 61 years of age is presented in Clinical Cardiology of Clinical Emergency County Hospital Timisoara with following complaints: fatigue, abdominal-pelvic pain and right lower limb, massive lower limb edema, with a difference of 8 cm between right and the left thigh, looking like phlegmatia alba dolens, gradually installed in the last 7 days.

Abdominal ultrasound in the right lower quadrant revealed a cystic, septate tumor of 7.2 cm in diameter,
containing mixed solid and liquid, respectively with hypoechoic, transonic and hyperechoic aspect, raising the suspicion of genital tumor, with ovarian location (confirmed by computed tomography).

Vascular ultrasound showed no Doppler signal (color and spectral) in common iliac vein and superficial femoral vein right.

Patient followed parenteral treatment with continuous infusion therapy with UFH, according to the aPTT values of 1.5 x 2 of normal values for 7 days, then the fractioned molecular weight heparin (enoxaparin) with significant remission of signs of deep vein thrombosis. Subsequently the patient was transferred to the oncology service and after chemotherapy had surgical intervention.

DISCUSSIONS

Mechanisms of DVT occurrence in cancer are multiple. First there is a subclinical activation of the coagulation system due to direct activation of coagulation system by malignant cells leading to production of thrombin. Tumor cells activate coagulation indirectly too, by stimulating the procoagulant activity of host cells including monocytes, platelets and endothelial cells. Chemotherapy further increases the risk of developing thrombosis. (4)

The main mechanisms by which tumor cells activated clotting are: induction of procoagulant state, or proagregante fibrinolytic release of proinflammatory cytokines and proangiogenic, direct interaction with host cells through the blood and vascular adhesion molecules, genetic defects associated with malignancy are involved in modulating expression of genes that control hemostasis, including TF, COX-2 and PAI-1 (5). TF growth occurring in many malignant tumors is attributed to the mutation of epidermal growth factor receptor (EGFR), RAS, p53 and PTEN. MET activation appears to increase the values of PAI-1 and COX-2 (6). Malignant cells synthesize proteins that act on the fibrinolytic system, including urokinase-type plasminogen activators and tissue type, plasminogen activator inhibitors 1 and 2 plasminogen activators and receptors. Note that causes malignant cells and platelet activation, probably through a mechanism dependent on COX-2 or by direct contact between cells. An increasing number of cytokines such as tumor cell secreted TNF-alpha, IL-1-beta and vascular endothelial growth factor may be associated with the development of DVT in patients with malignancy. Both TNF alpha and IL-1 beta increases the expression of TF and thrombomodulin production decreases, resulting in the development of a prothrombotic state in the vessel wall. These cytokines also increase fibrinolysis inhibitor PAI-1 production, thereby reducing the responsiveness antithrombotic endothelial cells. Additionally VEGF induces TF expression by endothelial cells. Cytokines also increase leukocyte chemotaxis and platelets to the vessel wall, favoring localized thrombosis and fibrin formation. The main role in the relationship between haemostatic system and malignant progression is played

Fig.10. B-mode abdominal ultrasound - oval inhomogeneous transonic and hiperecoic tumor formation about 7 cm

Fig.11. Venous Doppler ultrasound (cross section in the groin area) - the absence of Doppler signal in the right common femoral vein

Fig.12. Vascular color Doppler ultrasound (cross section at Scarpa’s triangle) - the absence of signal in right common femoral vein.
CONCLUSIONS

1. Patients with venous thrombosis associated to malignancies presented as predisposing factors, in addition to prothrombotic risk generated by thrombogenic tumor factors and surgery which existed in the history of 55% of patients, also the direct tumor compression and invasion of veins by local extension in 73% of cases.

2. We noted a high prevalence of proximal deep venous thrombosis in patients with cancer (73%) than those without cancer (69%).

3. There is not always a correlation between symptoms and extension of the deep vein thrombosis.

4. Vascular ultrasound is a rapid, non-invasive, without risk or discomfort to the patient method, useful in the diagnosis of deep vein thrombosis, thereby allowing the appropriate treatment and a reliable monitoring of the patient.

5. Venous ultrasound, both the B-mode and spectral and color Doppler, allows not only identifying the presence of thrombus and therefore positive diagnosis but also its expansion into deep and superficial venous system and the presence of residual blood flow, data which allow appreciating the prognosis and evolution of deep vein thrombosis.

6. The presence of a first episode of ilio-femoral deep vein thrombosis, especially in patients at risk, rise the necessity to investigate a possible malignant etiology.
References: