WHAT CAN HIDE BEHIND A DEEP VENOUS THROMBOSIS?
CASE REPORT

Irina Iuliana Costache¹,², Lucia Gușă¹, V. Fotea³, A. D. Costache⁴, B. Huzum⁷, Viviana Aursulesei¹,², A. O. Petriș¹,², D. Iliescu⁶, Delia Hînganu⁵∗
“Sf. Spiridon” County Clinical Emergency Hospital, Iasi, Romania
1. Department of Cardiology
“Grigore T. Popa” University of Medicine and Pharmacy Iasi, Romania
Faculty of Medicine
2. Department of Medical Specialties (I)
3. Department of Surgery (II)
4. Student
5. Department of Morpho-Functional Sciences (I)
“Arcadia” Hospital Iasi, Romania
6. Cardiology clinic
7. Ph.D. Student
∗Corresponding author. E-mail: delia_f24@yahoo.com

WHAT CAN HIDE BEHIND A DEEP VENOUS THROMBOSIS? CASE REPORT (Abstract): Deep venous thrombosis is frequently associated with various malignancies and, in particular, with pulmonary ones and is two times more common in patients with malignancies than those without. Recognition or diagnosis of a DVT as a paraneoplastic syndrome is important because it could represent the early manifestations of an occult cancer, allowing diagnosis at an initial stage. We are reporting the case of a 62-year-old patient who was hospitalized in the Cardiology Clinic with clinical symptoms of deep venous thrombosis at the right lower limb. The diagnosis was confirmed by the imaging methods: venous echo doppler and phlebography. Catheter directed thrombolysis was performed, followed by conventional anticoagulant treatment with favorable response. The patient was also investigated etiologically but without a clear result. After one month, chest radiography revealed a suggestive image for lung cancer, which required thoracic CT and bronchoscopy with biopsy. These investigations confirmed the diagnosis of left pulmonary cancer with carinal invasion, of the scirmamocellular type, with multiorganic secondary disseminations. The patient was directed to the Oncology Clinic. This case highlights the difficulty of making an etiologic diagnosis of deep venous thrombosis and a particular form of clinical onset of occult cancer. Since in the present case the occurrence of DVT preceded the diagnosis of the pulmonary cancer, the need to perform a screening of neoplasia is evident in case of any thromboembolic event occurring without an apparent cause, especially in the case of male patients. Key-words: PULMONARY CANCER, PARANEOPLASTIC SYNDROMS, DEEP VENOUS THROMBOSIS.

Paraneoplastic syndromes (PNS) represent a heterogeneous group of signs and symptoms associated with the progression of malignancy but not due to the direct
effects of primary tumor, adenopathy or metastasis (1). Recognition or diagnosis of a PNS is important because it could represent the early manifestations of an occult cancer, allowing diagnosis at an initial stage (2), can mimic metastatic disease and thus discourage the application of curative treatment for localized cancer, may also contribute to delaying treatment since complications of a cancer can be confused with a PNS (3). Cardiovascular paraneoplastic syndromes also include thrombophlebitis. Paraneoplastic thrombophlebitis (PNT) is one of the most suggestive manifestations under certain circumstances for cancer. They may be superficial and profound, occurring after the age of 50, more frequent in smokers and chronic alcohol users (4, 5, 6).

Venous thrombosis in patients diagnosed with malignant pathology is twice as high as patients without malignant pathology. Within this particular patient population, pulmonary cancer is the second in frequency regarding the relation with venous thrombosis second to hematological cancers (7, 8).

CASE REPORT

We are presenting the case of a 62-year-old patient, with no medical history of venous pathologies, who was a smoker until the age of 30 and an alcohol consumer, hospitalized in the Cardiology Clinic with clinical signs of edema in the lower right limb with hot tegument, erythema, pain in mole and functional impotence, suggestive for the diagnosis of deep venous thrombosis. The onset of the symptoms was 4 days prior. High-dose D-dimers (1,000-2,000 ng/mL) sustained the diagnosis.

The diagnosis was confirmed by imaging methods: venous echo doppler that revealed an almost complete thrombosis of the right femoral vein and almost complete venous thrombosis of the right popliteal vein. Phlebography of the right lower limb shows the opacity of the internal saphenous vein which communicates with the deep popliteal veins through the perforating veins. The femoral vein appears segmentally thrombosed, with dilated collateral muscular veins, with stasis and permeable anastomoses with the internal saphenous vein (fig. 1). The other veins were permeable.

![Fig. 1. A: Internal saphenous vein developing popliteal collateral circulation; B: Segmental thrombosis of femoral vein; C: The internal saphenous vein is still permeable throughout its entire length](image-url)
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Thrombolysis was subsequently conducted on the catheter with Rapillysin 1U/hr, followed by administration of Heparin 500 UI/hour. After 48 hours, phlebo-raphy showed reperfusion of calf veins in the upper 1/3 and femoral veins in the upper 1/3 of the thigh. The therapy was continued with conventional anticoagulant therapy (first heparin therapy, then oral anticoagulation) with favorable evolution.

At the same time, etiological investigations aimed at detecting a possible cause of deep venous thrombosis (DVT) were made, with the patient apparently not presenting prothrombotic risk factors (lack of varicose veins). Antiphospholipid antibodies were within normal range (Ig M = 10.3 U/mL, Ig G = 11.4 U/mL), and the thoracic radiography showed calcification of aortic knob; the suspicion of a possible type of alveolar filling syndrome arose although the patient was afebrile and did not have an inflammatory syndrome. Prostate ultrasound revealed a 21 mm hypoechogetic median node, but with negative prostate antigen, and upper digestive endoscopy revealed the presence of a hiatal hernia, corroborated with grade I esophagitis, atrophic gastritis in the corpus and fornix, and four inflammatory polyps with the diameter of 5-10 mm.

Electrocardiogram showed the presence of a major left bundle branch block, echocardiography revealed dilated cardiomyopathy with moderate dilated ventricle with diffuse hypokinesia (FEVS 40%), normal valves, minimal valvular regurgitation.

The patient was discharged from hospital with oral anticoagulant medication and recalled a month later to resume etiological investigations.

After a month, the patient presented with influenced general state, effort dyspnea, cough, dysphonia and dysphagia. The right lower limb exhibited (up to the lower third of the thigh) petechial lesions, confluent in the lower half of the calf and which did not disappear in vitropress.

The blood pressure was 155/80 mmHg and the blood count showed an increased GGT (207 U/L), moderate leukocytosis (GA = 12,500/mm³) associated with a fibrinogen of 4,64 g/L.

Thoracic radiography showed a larger predominantly enlarged mediastinum on the right; suprahilar adenopathy and a 2.7 cm round opacity in the middle left lung lobe, narrow tracheal lumen, which raised the suspicion of left bronchopulmonary neoplasia, requiring further investigations (fig. 2).

Fig. 2 A: initial posterior-anterior thoracic Rx, without changes in lung areas; B and C: postero-anterior thoracic and profile thoracic Rx after 30 days and presence of an opacity in the middle left lung lobe
The bronchoscopic examinations confirmed the diagnosis of pulmonary cancer into the left lung with the invasion of the tracheal carina. At the level of the left upper main bronchus a congestive infiltration process was observed, which interested the left primary bronchus from the origin and which then completely obstructed the inferior and superior left lobar bronchia. The bronchial biopsy revealed the mucosa with chronic inflammation and squamous metaplasia.

Computed topographies have been performed, confirming the presence of a 5.2/5 and 2/6 cm adenopathic tumor block, imprecisely delineated, located on the left primary bronchial emergence with posterior-lateral extension. The tumor was related anteriorly to the trachea, posteriorly to the esophagus, the vertebral body, the descending aorta and the azygos vein; medially is related to the mediastinal pleura, the medial wall of the main lower right bronchus and lateral to the right branch of the pulmonary artery (fig. 3). The interazigoaortic esophagus was almost occupied by a soft, non-homogeneous tissue mass with a cranial-caudal extension of about 6 cm, with the upper limit about 1 cm above the bifurcation of the trachea. The mediastinum was pushed to the left. There was another solid expanding formation of 2.5/3.0/1.0 cm in the topography of the right adrenal gland, hypodense after administration of the contrast substance. Another formation with the same characteristics was located on the left adrenal gland topography (1.5 cm).

Oncological consultation was required, and symptomatic cytostatic treatment was initiated. After the treatment, an improvement in dyspnea, coughing and dysphagia was noted. However, the progress of the diseases was rapidly progressive and ended with the patient’s death 14 months after oncological treatment began.

The particularities of this case are the appearance of deep vein thrombosis as a first sign of a bronchopulmonary cancer in a paraneoplastic syndrome associated with the appearance of a scumamocellular carcinoma with a relatively rapid evolution of the tumor and of the adenopathies within one month to a current non-smoker. The association between the cardiovascular pathology, smoking and alcohol consumption - dilatory ethanolic cardio-myopathy, with such a brief clinical expression is also very rare.

Fig. 3. High mediastinal adenopathies: A = on the sides of the trachea, B = posterior to the trachea, C = between pulmonary lobes; CT evaluation
DISCUSSION

Regarding thromboembolic events occurring in the neoplastic context, their incidence is 4 times higher than in the general population (9, 10, 11).

Nearly half of cases with migratory thrombophlebitis associate a neoplasia, and almost all of these are adenocarcinomas. Metastatic stages of cancers are associated with increased incidence of venous thromboembolism (12, 13, 14). Furthermore, chemotherapy increases the risk of venous thromboembolism 6 times than in the healthy population. Researchers (15) developed and validated a predictive model for the risk of venous thromboembolism (VTE) in patients undergoing chemotherapy (tab. I). The 0 score signifies a VTE risk below 1%, the intermediate score between 1-2% is associated with a 2% risk, and the score ≥ 3 signifies increased thrombotic risk (7%).

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>The risk of VTE associated with chemotherapy</th>
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<tbody>
<tr>
<td>Localization of neoplasia</td>
<td>2</td>
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<tr>
<td>- Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>- High risk (pulmonary, lymphoma, urogenital)</td>
<td>1</td>
</tr>
<tr>
<td>Pre-chemotherapy platelets ≥350 x 10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin &lt;10 g/dL or the use of erythropoiesis growth factors</td>
<td>1</td>
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<tr>
<td>Pre-chemotherapy leukocytes &gt; 11 x 10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>Body Mass Index ≥ 35 kg/m²</td>
<td>1</td>
</tr>
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A percentage of 10-20% of VTE patients hide a malignancy and it is a predictive independent marker of death in these patients. Studies have also shown that approximately 10% of patients with apparently no cause of THP will develop a neoplasm over the next 5-10 years, most of which are detected within the first 1-2 years (16).

The combination of neoplasia - VTE decreases survival, thrombotic events being reported as the second cause of mortality in this category of patients. Neoplastic patients with VTE have a much higher risk of bleeding events under anticoagulant treatment but also recurrence of thrombotic events with the same or another location (17).

To evoke a paraneoplastic mechanism in a thrombophlebitis, a direct tumor mechanism (extrinsic compression, venous invasion) and other circumstances such as radiotherapy must be eliminated. Differential diagnosis should eliminate a disseminated intravascular coagulation syndrome, frequent in neoplastic pathology. Dysphonia in this patient is based on the damage of the infraglottic filter of the vocal tract (18) and the dysphagia is determined by the compression exerted by the tumor on the thoracic esophagus.

Causes may be related to increased expression of tissue factor, activator of extrinsic coagulation mechanism, indirect induction of tumor-induced cytokines on tissue factor expression, tumor excretion of cysteine proteinase as direct procoagulant trigger of X factor, independent of factor VII, inducing a state of relative resistance to protein C or direct action of the platelets by tumor membrane fragments.

Along with a thorough clinical examination and a careful history, the following are necessary: hematological balance, venous echo doppler examination, phlebography, pletismography, thoracic radiography, superior digestive endoscopy, computed tomography, tumor markers.

The main treatment is intravenous therapy with heparin or low molecular weight heparins, an important feature of paraneoplastic deep venous thrombosis being the lack of response to oral anticoagulants. In the case of anticoagulant medication contraindications, it is possible to use a filter on the inferior vena cava.

The rapid unfavorable progression represents a characteristic of neoplastic patients who suffer also from deep vein thrombosis (19).
CONCLUSIONS
Since in the present case the occurrence of DVT preceded the diagnosis of the pulmonary cancer, the need to perform a screening of neoplasia is evident in case of any thromboembolic event occurring without an apparent cause, especially in the case of male patients.

REFERENCES