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DEEP VENOUS THROMBOSIS

Leonardo David Villacrés	MD. Medical Oncology Fellow "Universidad Central del Ecuador"
Carol Albacura*	MD. Medical Oncology Fellow "Universidad Central del Ecuador" *Corresponding Author
Selene Pallo	Medical Resident at "Hospital docente de Calderón" Quito-Ecuador
Daysi León Sanguano	Medical Resident at "Hospital de Especialidades de las Fuerza Armadas N°1" Quito-Ecuador
Marco León Montenegro	Medical Resident at "Hospital de Especialidades de las Fuerza Armadas N°1" Quito-Ecuador
Gabriela Claudio Pombosa	Medical Resident at "Hospital Carlos Andrade Marín" Quito-Ecuador
Mireya Vega	Internal Medicine Doctor at "Hospital Oncológico Solón Espinosa Ayala" Quito - Ecuador

INTRODUCTION

The oncological patient has as a particular condition an increased risk of developing deep vein thrombosis (DVT), which especially includes veins of the pelvis and lower limbs, can be complicated by serious conditions such as pulmonary thromboembolism (PE). (1-9)
The DVT of the lower limb is subdivided into two categories:

1. Distal, thrombi are confined to deep calf veins
2. Proximal, thrombosis compromises popliteal, femoral or iliac veins (10)

DVT also affects, although in a lesser proportion, superficial veins (saphenous veins) and other venous circulations present in the arms, brain, kidneys, liver, portal vein and mesenteric veins. (8)

It must be taken into account that this is a complex multifactorial disease in which interacts the tumor, as well as surgeries and medical treatment. (4-6,8,9)

The objective of the present review is to identify the risk factors in the oncological patient to develop DVT, in this way to use tools to prevent the development of the same, and to implement a management protocol before a thrombotic event.

EPIDEMIOLOGY OF DVT

The DVT is a problem of health care reaching a significant impact on mortality, morbidity and resource expenditure, it is the second cause of death in cancer patients. (11)

The incidence of DVT with respect to ethnic groups is higher in patients of African descent and lower in patients of Asian and Native American origin, with respect to people of Caucasian origin, its incidence varies between 104 to 183 per 100,000 people per year. (8)

Specifically, the association between thrombosis and cancer is well established, around 20% of cancer patients can develop a thromboembolic episode throughout the natural history of the tumor process. A predictive model of DVT risk in patients with cancer is the Khorana score. (8)

The DVT is predominantly greater in the elderly (8)

With respect to gender, it is greater in men than in women in a 1.2: 1 ratio.

The risk of developing DVT is higher in patients with cancer of the brain, pancreas, ovary, colon, stomach, lungs, kidney and bone tumors. (8)

The patients receiving immunosuppressive or cytotoxic therapy have a higher risk of developing DVT, including therapy with L-asparaginase, thalidomia, lenalidomide, and tamoxifen. (1-9).

PATHOPHYSIOLOGY OF DVT IN CANCER

The cancer cells per-se activate blood coagulation directly or indirectly, these can release procoagulant factors and activate endothelial cells, leukocytes, platelets, cytosines and can produce cysteine protease, activated X-factor, mucinous glycoproteins and circulation of tissue factor as well, As phospholipid microparticles, these biological elements lead to the formation of thrombin and the subsequent formation of fibrin. Thrombin together with tissue factor are in some way the mediating key in establishing the pathophysiology linked between cancer and thrombosis. (7,10)

The genetic mechanism responsible for the activation of some tumor oncogenes, such as K-RAS and the inactivation of tumor suppressor genes including TP53 can also modulate gene expression in the control core of hemostasis. (11)

INTRINSIC FACTORS:

The activation of thrombin and fibrin occurs directly by the release of procoagulants by the tumor cell, and indirectly, through the activation of endothelial cells, leukocytes and platelets by increasing proinflammatory cytokines and the production of factor Xa from the cysteine protease, mucinous glycoproteins and circulating tissue. (11,12).

Tissue factor (FT) physiologically initiates coagulation, its expression varies in different types of cancer and increases in advanced stages. (11)

The expression of FT by cancer cells is under the control of members of the EGFR family, RAS, TP53 and PTEN.(11)

The microparticles (submicrometric phospholipid vesicles derived from apoptotic and / or activated cells) and selectins (transmembrane molecules expressed on the surface of leukocytes and endothelial cells) can both initiate blood coagulation and allow the generation of thrombin. The microparticles and selectins provide a surface for the generation of leptin, a cytokine in adipose

tissue, which has been shown to lead to overexpression of TF in human MCF-7 breast cancer cells. (11)

Tumor cells can activate and add platelets, leading to the onset of thrombus formation through the process known as platelet aggregation-inducing tumor cells (CTIAP), these are correlated with the tendency of tumor-induced thrombogenesis and its metastatic potential. (13-22)

Vascular endothelial growth factor (VEGF) released by activated platelets is a proangiogenic protein, promotes vasculogenesis by stimulating endothelial migration and proliferation, additionally platelets release more proangiogenic proteins in patients with cancer. (13-22)

The white blood cell count is frequently elevated in patients with cancer. There was a 2.2 times higher risk of DVT with a white blood cell count greater than 11 x 10^{9} cells, as well as a platelet count greater than 350,000 ul. (3,4,7)

EXTRINSIC FACTORS

An increased risk of thrombosis is associated with alterations in normal blood flow, lesions in the vascular epithelium, and alteration in the components of the blood, the so-called Virchow triad. (11)

Extrinsic venous compression caused by locally advanced tumors and metastasis leads to venous stasis as well as the functional status of patients with advanced cancer that predisposes them to stay longer in bed increasing the risk of DVT, another factor is the use of central venous catheter. It alters the blood flow due to its invasive nature and the administration of drugs that will alter the vascular endothelium. (11)

CLINICAL DIAGNOSIS

A particular feature of the physical examination is pain in the calf or thigh "painful deep vein syndrome", unilateral edema with a difference in contralateral calf diameters, sensitivity, erythema, local heat and / or superficial venous dilatation.(23,24)

The pain of deep palpation of the calf muscles "Homans sign" is suggestive, but not diagnostic of DVT being unreliable. (23.24)

These characteristic findings can also be found in DVT of upper limbs. (23,24)

The physical examination may also reveal signs of hepatic vein thrombosis (Budd-Chiari syndrome), such as ascites and hepatomegaly.

Phlegmasia dolens cerulea - It is an uncommon form of massive proximal venous thrombosis (iliofemoral) associated with a high degree of morbidity and mortality. Signs and symptoms include sudden pain in the lower limb with significant edema, cyanosis, venous gangrene, compartment syndrome, and arterial compromise, often followed by circulatory collapse and shock. Delayed treatment can result in death or loss of the patient's limb (23)

DIAGNOSIS:

The clinical signs and symptoms of DVT are nonspecific and unreliable, if only clinical signs were used to diagnose DVT, 42% of patients would receive unnecessary treatment. However, the adequate combination of risk factors with clinical manifestations, adding to the existence or absence of an alternative diagnosis, can be used to classify patients into categories of high or low probability of suffering DVT, according to the prediction model of WELLS. (25)

Due to its high sensitivity (95%) and specificity (100%), Doppler ultrasound is the initial test indicated to detect the presence of DVT, particularly proximal to the knee, although phlebography remains the "golden test" for diagnosis, although it is reserved for certain special cases. (25)

Ultrasound detection of thrombosis in proximal lower limb veins shows a sensitivity of 97%, whereas in distal veins it is reduced to 73%. (25)

DIFFERENTIAL DIAGNOSIS

It is necessary to focus certain pathologies that rule out DVT, among these are described:

- Inguinal region: reactive or neoplastic lymph nodes, lymphangitis, iatrogenic vascular lesions, pseudoaneurysms and hematomas, or alterations of fat, femoral hernias or lipomas. (25)
- Crural region: traumatic muscle injuries, soft tissue tumors, deep fibromatosis, chronic compartment syndrome and myositis.(23-25)
- Popliteal region: Baker's cyst complications and popliteal artery aneurysms. (23-25)
- Distal region: musculoskeletal injuries associated with sports and tumors of the subcutaneous cellular tissue, both benign and malignant, as well as inflammatory processes of the subcutaneous cellular tissue. (23-25)

TREATMENT

Numerous international guides are available to provide guidance to health care providers to treat and prevent serious complications. In the majority of these guidelines, treatment with low molecular weight heparins (LMWH) is recommended for established DVT, it is of choice due to the decrease in the recurrence rate of the pathology during treatment. (26)

The appropriate dose of enoxaparin is stable at 1mg / kg of weight 2 times a day or 1.5mg / kg of weight once a day for the general population, there are no established data for patients with cancer to 1.5mg / kg of weight once a day .(1,2,4-6,9,26-28)

For dalteparin the dose is set at 200UI / Kg of weight in the first month and 150UI / Kg for the remaining 5 months, although this dose reduction can often be discussed.(1,2)

An important question often asked is how to identify the high-risk cancer patient for the onset of thromboprophylaxis.

Clinical practice guidelines such as ASCO, ESMO, NCCN recommend the use of instruments to identify the high risk cancer patient to develop DVT, a practical tool is the so-called "Khorana score" that was validated by the VIENNA CATS study, which considers a score greater than 3 as high risk, 1-2 intermediate risk and 0 low risk. (4-26)

With respect to treatment time, many guidelines reach a consensus that they should be treated for at least 6 months with LMWH, that their treatment be discontinued in the absence of active disease or that their oncologist does not have cancer treatment to follow, instead, it is recommended to extend the treatment time if the patient has active disease or needs to continue oncological treatment. (1,2,4-6,9,26-28)

In patients with DVT in upper limbs secondary to the use of a central venous catheter, the recommendation is the use of anticoagulants for at least 3 months for those who had a catheter removed and for those who did not follow the above considerations.(1,2,4,29)

The obese patients should be treated with LMWH doses according to their real weight and not calculate their ideal weight. (1,2,4-6,9,26-28)

With regard to oral anticoagulants, some special considerations should be taken into account, firstly the risk of bleeding increases of 12% with the use of LMWH to 21% with the use of warfarin, in addition studies suggest that in patients with active cancer develop resistance to warfarin. (4), without forgetting that warfarin interacts with chemotherapeutic drugs, so its use is recommended only if there is no adequate adherence to the use of LMWH, always adjusted to the INR.

In consideration of other oral anticoagulants such as Dabigatran,

ribaroxaba, apixaban, there are no studies in cancer patients so its use is not recommended. (1,2,4)

The use of enoxaparin is contraindicated in patients with active bleeding, a platelet count less than 50,000 U/L, although the literature mentions the use of LMWH with platelet count between 20,000 to 50,000 U/L but with recommendation grade 5D. (1,2)

In patients with cirrhosis the use of enoxaparin prophylactically can be used.(1,2)

With regard to renal function, there is no acceptable level of evidence between the use of LMWH or unfractionated heparins, however enoxaparin could have a less favorable biological effect than Tinzaparin or dalteparin. (1,2)

Thromboprophylaxis is suggested in post-operated patients with LMWH for at least 4 weeks if they have undergone major abdominal, pelvic, obese, previous history of DVT or those whose characteristics suggest high risk of developing thrombosis.(1,2)

Finally, the use of LMWH in a prophylactic manner (one daily dose of LMWH) is suggested in outpatients whose Khorana score is greater than 3 or who have advanced pancreatic cancer and thromboprophylaxis in hospitalized patients with active disease.(1,2)

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